Novel Serine Protease Genes Related to DPPIV

This application claims priority from U.S. provisional application Serial No. 60/240,117, filed October 12, 2000, the disclosure of which application is expressly incorporated by reference.

Field of the Invention

The present invention relates to novel serine proteases related to dipeptidyl peptidase IV (DPPIV), and to isolated nucleic acids coding for these proteases, all of which are useful for the discovery of new therapeutic agents, for measuring protease activity, and for determining the inhibitory activity of compounds against these proteases.

Background of the Invention

Proteases and peptidases are enzymes that catalyse the hydrolysis of peptidic amide bonds. Proteases play an important role in the regulation of biological processes in almost every life-form from bacteria to virus to mammals. They perform critical functions in, for example, digestion, blood clotting, apoptosis, activation of immune responses, zymogen activation, viral maturation, protein secretion and protein trafficking. They can be classified according to a number of criteria, such as site of action, substrate preference, and mechanism. So, for example, aminopeptidases act preferentially at the N-terminal residues of a peptide, while carboxypeptidases act preferentially at the C-terminus and endopeptidases act at sites removed from the two termini. Among the carboxy- and aminopeptidases, peptidyl peptidases cleave a single amino acid residue from the substrate, dipeptidyl peptidases cleave a dipeptide unit (two amino acids) from the substrate, and tripeptidases cleave three amino acids from the substrate. Substrate preference is frequently expressed in terms of the amino acid residue immediately N-terminal to the cleavage site. For example, trypsin-like peptidases will preferentially cleave a peptide next to a basic amino acid (arginine or lysine), i.e. where the bond hydrolysed is the Arg/Lys-Xaa bond. As another example, the chymotrypsin-like family of peptidases preferentially hydrolyse peptides adjacent to an aromatic residue. Mechanistically, peptidases are classified as being serine-dependent, cysteine-dependent, aspartic acid-dependent or zinc-dependent.

Because peptidases and proteases are involved in the regulation of many physiological processes, they are attractive targets for the development of therapeutic

agents. Protease and peptidase inhibitors are, for example, used in the treatment of hypertension, coagulation disorders, and viral infection.

Proteolytic enzymes that exploit serine in their catalytic activity are ubiquitous, being found in viruses, bacteria and eukaryotes. Over 20 families (denoted S1 - S27) of serine protease have been identified; these are grouped into 6 clans (SA, SB, SC, SE, SF and SG) on the basis of structural similarity and other functional evidence. Structures are known for four of the clans (SA, SB, SC and SE); these appear to be totally unrelated, suggesting at least four evolutionary origins of serine peptidases and possibly many more, Rawlings and Barrett, Meth. Enzymol. 244: 19-61 (1994).

The prolyl oligopeptidase family consists of a number of evolutionarily related peptidases whose catalytic activity seems to be provided by a charge relay system similar to that of the trypsin family of serine proteases, but which evolved by independent convergent evolution. A conserved serine residue has been shown experimentally (in *E. coli* protease II as well as in pig and bacterial PE) to be necessary for the catalytic mechanism. This serine, which is part of the catalytic triad (Ser, His, Asp), is generally located about 150 residues away from the C-terminal extremity of these enzymes (which are all proteins that contains about 700 to 800 amino acids).

One of the most intensively studied prolyl oligopeptidases is dipeptidyl peptidase IV (DPPIV, EC 3.414.5), a type II glycoprotein, which is the only well characterised dipeptidyl aminopeptidase known to be located on the outer side of plasma membranes. As indicated above, dipeptidyl aminopeptidases are characterised by their ability to cleave N-terminal dipeptides from a variety of small peptides. Dipeptidyl aminopeptidases show different substrate specificities and cellular localisation, suggesting different functions of each activity in peptide processing. DPPIV is characterised by its capacity to cleave N-terminal dipeptides containing proline or alanine as the penultimate residue. The DPPIV gene spans approximately 70 kb and contains 26 exons, ranging in size from 45 bp to 1.4 kb. The nucleotide sequence (3,465 bp) of the cDNA contains an open reading frame encoding a polypeptide comprising 766 amino acids. The nucleotides that encode the active site sequence (G-W-S-Y-G) are split between 2 exons. This clearly distinguishes the genomic organisation of the prolyl oligopeptidase family from that of the classic serine protease family.

DPPIV is widely distributed in mammalian tissues and is found in great abundance in the kidney, intestinal epithelium and placenta (Yaron, A. and Naider, F., Critical Reviews in Biochem. Mol. Biol. 1993 [1], 31). In the human immune system, the enzyme is expressed almost exclusively by activated T-lymphocytes of the $CD4^+$

type where the enzyme has been shown to be synonymous with the cell-surface antigen CD26. Although the exact role of DP-IV in human physiology is still not completely understood, recent research has shown that the enzyme clearly has a major role in human physiology and pathophysiology.

On human T cells, DPPIV expression appears late in thymic differentiation and is preferentially restricted to the $CD4^+$ helper/memory population, and CD26 can deliver a potent co-stimulatory T-cell activation signal. DPPIV, also known as T-cell activation antigen CD26, therefore plays an important role in the immune response via association with CD45 tyrosine phosphatase and, through its ability to bind adenosine deaminase (ADA) to the T-cell surface, protects the T-cell from adenosine-mediated inhibition of proliferation. Furthermore, the regulation of the function of chemokines by CD26/DPPIV appears to be essential for lymphocyte trafficking and infectivity of HIV strains. DPPIV has been associated with numerous functions including involvement in T-cell activation, cell adhesion, digestion of proline containing peptides in the kidney and intestines, HIV infection and apoptosis, and regulation of tumorigenicity in certain melanoma cells, Pethiyagoda et al., Clin. Exp. Metastasis 2000;18(5):391-400. DPPIV is also implicated in the endocrine regulation and metabolic physiology. More particularly, DPPIV cleaves the amino-terminal His-Ala dipeptide of GLP-1, generating a GLP-1 receptor antagonist, and thereby shortens the physiological response to GLP-1. Glucagon-like peptide-1 (GLP-1), an incretin that induces glucose-dependent insulin secretion, is rapidly degraded by DPPIV, and since the half-life for DPPIV cleavage is much shorter than the half-life for removal of GLP-1 from circulation, a significant increase inGLP-1 bioactivity (5- to 10- fold) is anticipated from DPP-IV inhibition. Inhibitors of DPPIV are currently being studied in the clinic as potential therapeutic agents for type 2 diabetes and impaired glucose tolerance.

Various different inhibitors of DPPIV were known in 1993. One of these is a suicide inhibitor N-Ala-Pro-O-(nitrobenzoyl-) hydroxylamine. Another is a competitive inhibitor: e-(4-nitro) benzoxycarbonyl-Lys-Pro, and another is a polyclonal rabbit anti-porcine kidney DPPIV immunoglobulin. Others have since been developed and are described in detail in U.S. Patents Nos. 5,939,560, 6,110,949m 6,011,155 and 5,462,928.

In addition to, but independent of, its serine type catalytic activity, DPPIV binds closely to the soluble extracellular enzyme adenosine deaminase (ADA), acting as a receptor and is thought to mediate signal transduction. DPPIV structure is characterized by two extracellular domains, an α/β fold hydrolase domain and a 7-blade beta-propeller domain consisting of repeated beta sheets of about 50 amino acids. Recently it has been

shown that, besides selecting substrates by size, the beta-propeller domain, containing 10 of the 12 highly conserved cysteine residues, contributes to catalysis of the peptidase domain. In addition, the cysteine-rich domain is responsible for DPPIV-binding to collagen I and to extracellular ADA. DPPIV is also reported to play a role in fibronectin-mediated interactions of cells with extracellular matrix. Recent studies show that the protease activity of DPPIV is not required for its anti-invasive activity because mutants of DPPIV that lack the extracellular serine protease activity maintain such activity.

A number of proteins that share similarities with DPPIV have been reported in the literature. Several of these proteins have been cloned including DPP-I, DPP-II, DPP-III, DPP-X and fibroblast activation protein (FAP). These have been identified and characterised either by molecular cloning and functional studies of expressed proteins or as biochemical activities in tissue extracts. DPPIV-beta and other novel peptidases with functional similarities to DPPIV are not yet cloned. The identification, characterization and/or appropriate classification of further members of the family of prolyl oligopeptidases, the elucidation of their physiological (and particularly pathophysiological) role, and the application of that knowledge to the development of new therapeutic agents are significant challenges.

Summary of the Invention

The present invention provides proteins with prolyloligopeptidase (post-proline cleaving) activities that constitute three novel members of a family of proteins related to DPPIV, including the full-length proteins, alternative splice forms, subunits, and mutants, as well as nucleotide sequences encoding the same. The present invention also provides methods of screening for substrates, interacting proteins, agonists, antagonists or inhibitors of the above proteins, and furthermore to pharmaceutical compositions comprising the proteins and/or mutants, derivatives and/or analogues thereof and/or ligands thereto.

These novel proteins having significant sequence homology to DPPIV are termed dipeptidyl peptidase IV-related protein-1, 2 & 3 (DPRP-1, DPRP-2 and DPRP-3). The amino acid sequences of DPRP-1, DPRP-2 and DPRP-3 are given in SEQ. ID NOS:1, 3 and 5 respectively. Further disclosed are nucleic acid sequences coding for these proteins (SEQ. ID NOS:2, 4 and 6). Table 1 illustrates the homology (i.e. similarity) between the novel proteins DPRP-1, DPRP-2 and DPRP-3 and other known serine proteases.

Table 1 – Comparison of the sequences of these three novel proteins with DPPIV and other Clan SC, Family S9 members and Subfamily B members

Protease Family	Protease name	No. of a.a.	Homology with DPPIV	TM region	Ser-Asp-His Triad	Gene location	Optimal pH
Clan CA, Family C1	DPPI	463	N	N	N	11q14.1-q14.3	-
Clan SC, Family S28	DPPII	500	N	Y	N	-	4.5-6.0
	QPP	492	N	N	N	-	4.5-7.5
	PCP	496	N	N	N	-	-
Unassigned	DPPIII	737	N	N	N	-	-
Clan SC, Family S9, Subfamily B	DPPIV	766	100	Y	Y	2q24.3	7.5-8.0
	DPPVI	865	52	Y	Mutation	7	-
	FAP	760	70	Y	Y	2q23	7.5-8.0
	DPRP-1	882	41	N	Y	15q22.1-15q22.2	7.5-8.0
	DPRP-2	864	39	N	Y	19p13.3	7.5-8.0
	DPRP-3	796	54	Y	Mutation	2q12.3-2q14.1	-

The greatest homology between DPRP-1, DPRP-2 and DPPIV is seen in the C-terminal sequences. On the basis of sequence homology with DPPIV (see Figure 1), one might predict that these DPRP proteins would have functions that include, but are not limited to, roles as enzymes. Cloning, expression, biochemical and molecular characterization have confirmed this hypothesis.

The expression pattern of DPRPs and the localization to specialized epithelial cells and plasma cells (Leydig cells, prostate epithelial cells, lymphocytes, B cells) is consistent with a role in differentiation, proliferation and inflammation. The localization of the DPRP-1 gene in hormone sensitive cancers (breast, prostate, testicular), tissues regulated by testosterone and the abundant expression in poorly differentiated cancers, demonstrate that DPRP-activating or inhibiting molecules will have numerous therapeutic applications in the treatment of disorders characterized by disregulated growth, differentiation and steroid or polypeptide hormone synthesis and degradation. Data disclosed herein supports the hypothesis that DPRP-1 and DPRP-2 are involved in the regulation of proliferation of *in vitro* models of prostate and testis cancer well known to those skilled in the art.

DPRP-1 and DPRP-2 activities described herein and their expression patterns are compatible with their having functional roles as physiological regulators of the immune and neuroendocrine systems through the enzymatic modification of biochemical mediators like peptides and chemokines. The numerous functions previously described

for DPPIV based upon the use of inhibitors may be due in part to its action and that of similar proteins, like the DPRPs. Therefore, the discovery of selective and potent inhibitors of DPPIV, of the DPRPs and of other related proteases like FAP is considered central to achieving effective and safe pharmaceutical use of these and any newly identified serine protease inhibitors, as well as other active compounds that modify the function(s) of such proteins.

The invention thus provides novel proteins or polypeptides, the nucleic acids coding therefor, cells which have been modified with the nucleic acid so as to express these proteins, antibodies to these proteins, a screening method for the discovery of new therapeutic agents which are inhibitors of the activity of these proteins (or which are inhibitors of DPPIV and not of the proteins), and therapeutic agents discovered by such screening methods. The novel proteins and the nucleic acids coding therefor can be used to discover new therapeutic agents for the treatment of certain diseases, such as for example, reproductive, inflammatory and metabolic disorders and also in the preparation of antibodies with therapeutic or diagnostic value.

In accordance with one aspect of the present invention, there are provided novel, mature, biologically active proteins, principally of human origin. Such proteins may be isolated in small quantities from suitable animal (including human) tissue or biological fluids by standard techniques; however, larger quantities are more conveniently prepared in cultures of cells genetically modified so as to express the protein.

In accordance with another aspect of the present invention, there are provided isolated nucleic acid molecules encoding polypeptides of the present invention including mRNAs, DNAs, cDNAs, genomic DNAs thereof.

In accordance with a further aspect of the present invention, nucleic acid probes are also provided comprising nucleic acid molecules of sufficient length to specifically hybridize to a nucleic acid sequence of the present invention.

In accordance with a still further aspect of the present invention, processes utilizing recombinant techniques are provided for producing such polypeptides useful for *in vitro* scientific research, for example, synthesis of DNA and manufacture of DNA vectors. Processes for producing such polypeptides include culturing recombinant prokaryotic and/or eukaryotic host cells that have been transfected with DNA vectors containing a nucleic acid sequence encoding such a polypeptide and/or the mature protein under conditions promoting expression of such protein and subsequent recovery of such protein or a fragment of the expressed product.

In accordance with still another aspect, the invention provides methods for using DPRP polypeptides and polynucleotides, including the treatment of infections, such as bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2, pain, diabetes, precocious puberty, infertility, obesity, anorexia, bulimia, Parkinson's disease, acute heart failure, hypotension, hypertension, urinary retention, osteoporosis, angina pectoris, myocardial infarction, stroke, ulcers, asthma, allergies, benign prostatic hypertrophy, cancers including hormone-sensitive and androgen-independent cancers, migraines, vomiting, psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, depression, dementia, and severe mental retardation, and dyskinesias, hereinafter collectively referred to as "the Diseases".

In accordance with yet another aspect of the present invention, there is provided a process for utilizing such polypeptides, or polynucleotides encoding such polypeptides, for the discovery of compounds that inhibit the biological activity of the mature proteins thereof, e.g. by cleaving an N-terminal dipeptide, and such inhibitors are thus also provided.

These and other aspects of the present invention should be apparent to those skilled in the art from the detailed description which follows.

Brief Description of the Drawings

FIGS. 1A and 1B show the co-linear alignment of DPRP-1, DPRP-2, DPRP-3 and DPPIV, with shading being supplied to indicate the same (black) or similar (gray) amino acid residues at a particular location.

FIG. 2 is similar to FIG. 1 and shows co-linear alignment of human and mouse DPRP-2.

FIG. 3 is a graph which shows the effects of various tetrapeptide amide inhibitors on dipeptidyl peptidase enzyme activity.

FIGS. 4A-4C show the effects of three inhibitor compounds on the proliferation of PC3 prostate cancer cell lines at various doses.

Detailed Description of the Preferred Embodiments

In accordance with an aspect of the present invention, there are provided isolated nucleic acid sequences (polynucleotides), which encode the mature polypeptides having the deduced amino acid sequences of the three DPRP's (SEQ ID NOS:1, 3 and 5).

The polynucleotides of this invention were discovered using a human testis cDNA library (DPRP-1), a human colon library (DPRP-2) and a human hypothalamus

cDNA library (DPRP-3). Isolated nucleic acid for DPRP-1 contains an open reading frame encoding a protein of approximately 882 amino acids in length which is structurally related to human DPPIV, showing 26% identity, and 41% similarity over the entire human DPPIV protein sequence. Isolated nucleic acid for DPRP-2 contains an open reading frame encoding for a protein of approximately 864 amino acids, which is 39% similar to the entire DPPIV amino acid sequence. Analysis of DPRP-1 and DPRP-2 primary amino acid sequence using hydrophobicity plots predicts that these two proteins do not have a transmembrane domain. Despite this fact, it is possible that these intracellular serine proteases are secreted upon cellular activation. Quiescent cell proline dipeptidase (QPP) is a serine protease that is targeted to intracellular vesicles that are distinct from lysosomes (Chiravuri M, et al., J. Immunol. 2000 Nov 15;165(10):5695-702). This hypothesis expands the potential site(s) and scope of DPRP-1 and DPRP-2 involvement in mechanisms for post-translational regulation of chemokines, cytokines, peptides and polypeptides. The full length DPRP-3 sequence contains 796 amino acids, a signal peptide from 1 to 48, and a transmembrane domain between 34 and 56. The mature protein is predicted to be a type II membrane protein and may be cleaved to produce a soluble form. The amino acid sequence is set forth in SEQ ID NO:5 , which was deduced from SEQ ID NO:6 and has 54% similarity with DPPIV.

Amino acid sequence alignments of these polypeptides with members of the prolyloligopeptidase enzyme subfamily S9B show that all three DPRP proteins have overall sequence and structural homology to DPPIV and FAP. DPRPs are predicted to be a members of the enzyme Clan SC (Serine nucleophile) with catalytic residues in the order Ser, Asp, His and the active site sequence (G-W-S-Y-G).

Table 2. Homology (i.e. similarity) between DPRP-1, DPRP-2, DPRP-3 and members of the prolyl oligopeptidase family S9B enzymes.

DPPIV	DPRP-1	DPRP-2	DPRP-3	FAP	DPPVI
41					
39	74				
54	39	40			
70	41	39	52		
52	40	42	68	54	

DPRP-1, DPRP-2 and DPRP-3 do not exhibit sequence similarity with any members of the classical serine protease families, chymotrypsin and subtilisin. The order

of the catalytic triad residues is different in the three main related SC clan families: His-Asp-Ser in chymotrypsin, Asp-His-Ser in subtilisin and Ser-Asp-His in the prolyl oligopeptidases.

As shown in Table 2, DPRP-3 has the highest homology with DPPVI (68% homology and 51% identity). Wada et al isolated cDNA clones for DPPVI, a DPPIV-related protein, from bovine, rat (Wada et al., Proc. Nat. Acad. Sci. 89: 197-201. (1992)) and human (Yokotani et al., Hum. Molec. Genet. 2:1037-1039 (1993)) brain libraries. They demonstrated that, unlike DPPIV, the catalytic triad in DPPVI does not have the first serine residue. In DPRP-3 two of the amino acids in the catalytic triad characteristic of the serine protease family are conserved. However, the serine residue itself is replaced by glycine. While the absence of the serine residue is likely to prevent protease activity at this site, it is possible that multiple other functions mediated by other functional domains of the protein remain intact.

As briefly described above, DPPIV is a multifunctional molecule that exerts important functions depending on the expressed cells and tissues, in addition to its catalytic activity as a peptidase. DPRP-3 and DPPVI are also likely to maintain multiple functions despite the absence of an intact catalytic triad. For example, DPPVI has been implicated in the regulation of neuronal plasticity. DPPVI is highly expressed in the hippocampus, thalamus, hypothalamus and stiatum. In addition, developmental arrest and embryonic lethality of *rump white Rw/Rw* embryos is thought to be due to disruption of the DPPIV gene. *Rw* mutation is associated with a chromosomal inversion spanning 30 cM of the proximal portion of mouse chromosome 5. Genomic analysis of the DPPVI gene on the *Rw* chromosome places the inversion breakpoint in the coding region resulting in loss of a significant fraction of the C-terminal region, Hough R.B. et al., Proc. Nat. Acad. Sci., 95, 13800-13805 (1998).

The human DPRP-1 gene, predicted to be 32668bp in length, has at least 22 exons and eight transcripts. It maps to chromosome 15 (NT_010265) at position 15q21.1 – 15q22.1. The lengths of predicted alternative splice variant transcripts vary between 602bp and 4523bp (see SEQ ID NOS: 7-22). This is in agreement with the multiple transcripts observed by Northern blot analysis (See Example 2). ESTs representing the transcripts were found in numerous tissues including senescent fibroblasts, T-lymphocytes, germinal center B-cells, germ cell seminoma, testis, melanocytes, uterus, ovary breast, multiple sclerosis lesions, pancreas and placenta.

Human DPRP-2 belongs to a gene with at least 27 exons and nine splice variants (see SEQ ID NOS:23-40). One SNP was observed in the 3' UTR. (88% (37) C vs. 12%

(5) T). The DPRP-2 gene maps to region 19p13.3 of chromosome 19. This location is host to a number of disease markers and is associated with various disorders including hypocalciuric hypercalcemia, type II cerebellar ataxia, muscular dystrophy, convulsions, susceptibility to atherosclerosis, psoriasis, ectodermal dysplasia, and acute myeloid leukemia. In agreement with the ubiquitous distribution of the mRNA observed by Northern blot analysis (see Example 2), DPRP-2 was expressed in a wide variety of tissues upon examination of EST's coverage (e.g. over 64 EST's expressed in liver, spleen, muscle, melanocytes, heart, lung, placenta, skin, pancreas, stomach, brain parathyroid gland).

Human DPRP-3 belongs to a gene with at least 23 exons and two splice variants (see SEQ ID NOS:41-44). The gene maps to chromosome 2 (NT_005445) at position 2q12.3-2q14.1. Transcripts for DPRP-3 did not show as wide a distribution as DPRP-1 and DPRP-2. As shown by Northern blot in Example 2, DPRP-3 expression is restricted to brain and pancreas. ESTs representing the DPRP-3 mRNA were abundant in tissue derived from multiple sclerosis lesions, hypothalamus, whole brain and nerves, with a few transcripts being found in uterus and colon.

The relationships among human and rodent proteases in clan SC, including DPRP-1 DPRP-2 and DPRP-3, were analyzed using Neighbor Joining method (NJ), see Saitou and Nei, Mol. Biol. Evol., 4, 406-525 (1987). Phylogenetic analysis shows that among the S9 proteases, DPRP-1 and DPRP-2, both lacking a transmembrane domain, are distinguished from DPPIV and its closely related proteins like FAP. Similarity is shown however between DPPIV and FAP and between DPRP-3 and DPPVI, which are all type II membrane proteins.

A database search for additional DPRP-related genes revealed the presence of a murine sequence related to DPRP-1. Alignment of this mouse sequence with the novel human proteases shows that the mDPRP-1 displays considerable homology with its human counterpart (FIG. 2). One skilled in the art will readily recognize that the novel mouse protease gene can be isolated using the sequence information disclosed herein and can be readily incorporated into one of the routinely used expression constructs which are well known in the art. Use of this disclosed sequence by those skilled in the art to generate a transgenic mouse model will employ development of gene-targeting vectors, for example, that result in homologous recombination in mouse embryonic stem cells. The use of knockout mice in further analysis of the function of DPRP genes is a valuable tool.

The polynucleotides of the present invention may be in the form of RNA or in the form of DNA; DNA should be understood to include cDNA, genomic DNA, and synthetic DNA. The DNA may be double-stranded or single-stranded and, if single-stranded, may be the coding strand or non-coding (antisense) strand. The coding sequence which encodes the mature polypeptide may be identical to the coding sequence shown in SEQ ID NOS:2, 4 and 6 respectively, or it may be a different coding sequence encoding the same mature polypeptide, as a result of the redundancy or degeneracy of the genetic code or a single nucleotide polymorphism. For example, it may also be an RNA transcript which includes the entire length of any one of SEQ ID NOS:2, 4 and 6.

The polynucleotides which encode the mature proteins of SEQ ID NOS:1, 3, 5, respectively, may include but are not limited to the coding sequence for the mature protein alone; the coding sequence for the mature polypeptide plus additional coding sequence, such as a leader or secretory sequence or a proprotein sequence; and the coding sequence for the mature protein (and optionally additional coding sequence) plus non-coding sequence, such as introns or a non-coding sequence 5' and/or 3' of the coding sequence for the mature protein.

Thus, the term "polynucleotide encoding a polypeptide" or the term "nucleic acid encoding a polypeptide" should be understood to encompass a polynucleotide or nucleic acid which includes only coding sequence for the mature protein as well as one which includes additional coding and/or non-coding sequence. The terms polynucleotides and nucleic acid are used interchangeably.

The present invention also includes polynucleotides where the coding sequence for the mature protein may be fused in the same reading frame to a polynucleotide sequence which aids in expression and secretion of a polypeptide from a host cell; for example, a leader sequence which functions as a secretory sequence for controlling transport of a polypeptide from the cell may be so fused. The polypeptide having such a leader sequence is termed a preprotein or a preproprotein and may have the leader sequence cleaved, by the host cell to form the mature form of the protein. These polynucleotides may have a 5' extended region so that it encodes a proprotein, which is the mature protein plus additional amino acid residues at the N-terminus. The expression product having such a prosequence is termed a proprotein, which is an inactive form of the mature protein; however, once the prosequence is cleaved an active mature protein remains. Thus, for example, the polynucleotides of the present invention may encode mature proteins, or proteins having a prosequence, or proteins having both a prosequence and a presequence (leader sequence).

The polynucleotides of the present invention may also have the coding sequence fused in frame to a marker sequence which allows for purification of the polypeptides of the present invention. The marker sequence may be a polyhistidine tag, a hemagglutinin (HA) tag, a c-myc tag or a V5 tag when a mammalian host, e.g. COS-1 cells, is used. The HA tag would correspond to an epitope derived from the influenza hemagglutinin protein (Wilson, I., et al., Cell, 37:767 (1984)), and the c-myc tag may be an eptitope from human Myc protein (Evans, G.I. et al., *Mol. Cell. Biol. 5*: 3610-3616 (1985)).

The term "gene" means the segment of DNA involved in producing a polypeptide chain; it includes regions preceding and following the coding region (leader and trailer) as well as intervening sequences (introns) between individual coding segments (exons). The term "significant sequence homology" is intended to denote that at least 25%, preferably at least 40%, of the amino acid residues are conserved, and that, of the non-conserved residues, at least 40% are conservative substitutions.

Fragments of the full-length genes of the present invention may be used as a hybridization probe for a cDNA library to isolate full-length cDNA as well as to isolate other cDNAs which have significant sequence homology to the gene and will encode proteins or polypeptides having similar biological activity or function. By similar biological activity or function, for purposes of this application, is meant the ability to cleave an N-terminal dipeptide having Ala or Pro as the penultimate residue or other amino acids. Such a probe of this type has at least 14 bases (at least 14 contiguous nucleotides from one of SEQ ID NOS:2, 4 or 6), preferably at least 30 bases, and such may contain, for example, 50 or more bases. Such probe may also be used to identify a cDNA clone corresponding to a full-length transcript and/or a genomic clone or clones that contains the complete gene, including regulatory and promoter regions, exons, and introns. Labelled oligonucleotides having a sequence complementary to that of the gene of the present invention are useful to screen a library of human cDNA, genomic DNA or mRNA to locate members of the library to which the probe hybridizes. As an example, a known DNA sequence may be used to synthesize an oligonucleotide probe which is then used in screening a library to isolate the coding region of a gene of interest.

The present invention is considered to further provide polynucleotides which hybridize to the hereinabove-described sequences wherein there is at least 70%, preferably at least 90%, and more preferably at least 95% identity or similarity between the sequences, and thus encode proteins having similar biological activity. Moreover, as known in the art, there is "similarity" between two polypeptides when the amino acid sequences contain the same or conserved amino acid substitutes for each individual

residue in the sequence. Identity and similarity may be measured using sequence analysis software (e.g., Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705). The present invention particularly provides such polynucleotides which hybridize under stringent conditions to the hereinabove-described polynucleotides. As herein used, the term "stringent conditions" means conditions which permit hybridization between polynucleotides sequences and the polynucleotide sequences of SEQ ID NOS:2, 4 and 6 where there is at least about 70% identity. Suitably stringent conditions can be defined by, e.g., the concentrations of salt or formamide in the prehybridization and hybridization solutions, or by the hybridization temperature, and are well known in the art. In particular, stringency can be increased by reducing the concentration of salt, by increasing the concentration of formamide, and/or by raising the hybridization temperature.

For example, hybridization under high stringency conditions may employ about 50% formamide at about 37°C to 42°C, whereas hybridization under reduced stringency conditions might employ about 35% to 25% formamide at about 30°C to 35°C. One particular set of conditions for hybridization under high stringency conditions employs 42°C, 50% formamide, 5x. SSPE, 0.3% SDS, and 200 µg/ml sheared and denatured salmon sperm DNA. For hybridization under reduced stringency, similar conditions as described above may be used in 35% formamide at a reduced temperature of 35°C. The temperature range corresponding to a particular level of stringency can be further narrowed by calculating the purine to pyrimidine ratio of the nucleic acid of interest and adjusting the temperature accordingly. Variations on the above ranges and conditions are well known in the art. Preferably, hybridization should occur only if there is at least 95%, and more preferably at least 97%, identity between the sequences. The polynucleotides which hybridize to the hereinabove described polynucleotides in a preferred embodiment encode polypeptides which exhibit substantially the same biological function or activity as the mature protein encoded by one of the cDNAs of SEQ ID NOS:2, 4 and 6.

As mentioned, a suitable polynucleotide probe may have at least 14 bases, preferably 30 bases, and more preferably at least 50 bases, and will hybridize to a polynucleotide of the present invention which has an identity thereto, as hereinabove described, and which may or may not retain activity. For example, such polynucleotides may be employed as a probe for hybridizing to the polynucleotides of SEQ ID NOS:2, 4 and 6 respectively, for example, for recovery of such a polynucleotide, or as a diagnostic

probe, or as a PCR primer. Thus, the present invention includes polynucleotides having at least a 70% identity, preferably at least a 90% identity, and more preferably at least a 95% identity to a polynucleotide which encodes the polypeptides of SEQ ID NOS:1, 3 and 5 respectively, as well as fragments thereof, which fragments preferably have at least 30 bases and more preferably at least 50 bases, and to polypeptides encoded by such polynucleotides.

As is well known in the art, the genetic code is redundant in that certain amino acids are coded for by more than one nucleotide triplet (codon), and the invention includes those polynucleotide sequences which encode the same amino acids using a different codon from that specifically exemplified in the sequences herein. Such a polynucleotide sequence is referred to herein as an "equivalent" polynucleotide sequence. The present invention further includes variants of the hereinabove described polynucleotides which encode for fragments, such as part or all of the mature protein, analogs and derivatives of one of the polypeptides having the deduced amino acid sequence of SEQ ID NOS:1, 3 and 5 respectively. The variant forms of the polynucleotides may be a naturally occurring allelic variant of the polynucleotides or a non-naturally occurring variant of the polynucleotides. For example, the variant in the nucleic acid may simply be a difference in codon sequence for the amino acid resulting from the degeneracy of the genetic code, or there may be deletion variants, substitution variants and addition or insertion variants. As known in the art, an allelic variant is an alternative form of a polynucleotide sequence which may have a substitution, deletion or addition of one or more nucleotides that does not substantially alter the biological function of the encoded polypeptide.

The present invention further includes polypeptides which have the deduced amino acid sequence of SEQ ID NOS:1, 3 and 5, as well as fragments, analogs and derivatives of such polypeptides. The terms "fragment," "derivative" and "analog", when referring to the polypeptides of SEQ ID NOS:1, 3 and 5, means polypeptides that retain essentially the same biological function or activity as such polypeptides. An analog might, for example, include a proprotein which can be activated by cleavage of the proprotein portion to produce an active mature protein. The polypeptides of the present invention may be recombinant polypeptides, natural polypeptides or synthetic polypeptide; however, they are preferably recombinant polypeptides, glycosylated or unglycosylated.

The fragment, derivative or analog of a polypeptide of SEQ ID NOS:1, 3 and 5 respectively, may be (i) one in which one or more of the amino acid residues is

substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which additional amino acids are fused to the mature protein, such as a leader or secretory sequence or a sequence which is employed for purification of the mature polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art to provide upon the basis of the teachings herein.

The polypeptides and polynucleotides of the present invention should be in an isolated form, and preferably they are purified to substantial homogeneity or purity. By substantial homogeneity is meant a purity of at least about 85%.

The term "isolated" is used to mean that the material has been removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally occurring polynucleotide or polypeptide present in a living animal is not considered to be isolated, but the same polynucleotide or polypeptide, when separated from substantially all of the coexisting materials in the natural system, is considered isolated. For DNA, the term includes, for example, a recombinant DNA which is incorporated into a vector, into an autonomously replicating plasmid or virus, or into the genomic DNA of a prokaryote or eukaryote; or which exists as a separate molecule (e.g., a cDNA or a genomic or cDNA fragment produced by polymerase chain reaction (PCR) or restriction endonuclease digestion) independent of other sequences. It also includes a recombinant DNA which is part of a hybrid gene encoding additional polypeptide sequence, e.g., a fusion protein. Further included is recombinant DNA which includes a portion of the nucleotides shown in one of SEQ ID NO:2,4 or 6 which encodes an alternative splice variant of the DPRP. Various alternative splice variants are exemplified in SEQ ID NOS:8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44 and 46.

The polypeptides of the present invention include any one of the polypeptide of SEQ ID NOS:1, 3 and 5 (in particular the mature protein), as well as polypeptides which have at least 70% similarity (e.g. preferably at least 60% and more preferably at least 70% identity) to one of the polypeptides of SEQ ID NOS:1, 3 and 5, more preferably at least 90% similarity (e.g. preferably at least 90% identity) to one of the polypeptides of SEQ ID NOS:1, 3 and 5, and most preferably at least 95% similarity (e.g. preferably at least 95% identity) to one of the polypeptides of SEQ ID NOS:1, 3 and 5. Moreover,

they should preferably include exact portions of such polypeptides containing a sequence of at least 30 amino acids, and more preferably at least 50 amino acids.

Fragments or portions of the polypeptides of the present invention may be employed as intermediates for producing the corresponding full-length polypeptides by peptide synthesis. Fragments or portions of the polynucleotides of the present invention may also be used to synthesize full-length polynucleotides of the present invention.

The present invention also includes vectors which include such polynucleotides, host cells which are genetically engineered with such vectors and the production of polypeptides by recombinant techniques using the foregoing. Host cells are genetically engineered (transduced or transformed or transfected) with such vectors which may be, for example, a cloning vector or an expression vector. The vector may be, for example, in the form of a plasmid, a viral particle, a phage, etc. The engineered host cells can be cultured in conventional nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the genes of the present invention. The culture conditions, such as temperature, pH and the like, are those commonly used with the host cell selected for expression, as well known to the ordinarily skilled artisan.

The polynucleotides of the present invention may be employed for producing polypeptides by recombinant techniques. Thus, for example, the polynucleotides may be included in any one of a variety of expression vectors for expressing polypeptides. Such vectors include chromosomal, nonchromosomal and synthetic DNA sequences, e.g., derivatives of SV40; bacterial plasmids; phage DNA; baculovirus; yeast plasmids; vectors derived from combinations of plasmids and phage DNA, viral DNA such as vaccinia, adenovirus, fowl pox virus, and pseudorabies. However, any other vector may be used as long as it is replicable and viable in the host.

The appropriate DNA sequence may be inserted into the vector by any of a variety of procedures. In general, the DNA sequence is inserted into an appropriate restriction endonuclease site(s) by procedures well known in the art, which procedures are deemed to be within the scope of those skilled in this art.

The DNA sequence in the expression vector is operatively linked to an appropriate expression control sequence(s) (promoter) to direct mRNA synthesis. As representative examples of such promoters, there may be mentioned: LTR or SV40 promoter, the *E. coli.* lac or trp, the phage lambda P.sub.L promoter and other promoters known to control expression of genes in prokaryotic or eukaryotic cells or their viruses. The expression vector should also contain a ribosome binding site for translation initiation and a transcription terminator. The vector may also include appropriate

sequences for amplifying expression. In addition, the expression vectors preferably contain one or more selectable marker genes to provide a phenotypic trait for selection of transformed host cells, such as dihydrofolate reductase or neomycin-resistance for eukaryotic cell culture, or such as tetracycline- or ampicillin-resistance in *E. coli*.

The vector containing the appropriate DNA sequence as hereinabove described, as well as an appropriate promoter or control sequence, may be employed to transform an appropriate host to permit the host to express the protein. As representative examples of appropriate hosts, there may be mentioned: bacterial cells, such as *E. coli*, Streptomyces, Salmonella typhimurium; fungal cells, such as yeast; insect cells, such as Drosophila S2 and Spodoptera Sf9; animal cells, such as CHO, COS or Bowes melanoma; adenoviruses; plant cells, etc. The selection of an appropriate host is deemed to be within the scope of those skilled in the art from the teachings herein.

Synthetic production of nucleic acid sequences is well known in the art as is apparent from CLONTECH 95/96 Catalogue, pages 215-216, CLONTECH, 1020 East Meadow Circle, Palo Alto, Calif. 94303. Thus, the present invention also includes expression vectors useful for the production of the proteins of the present invention

The present invention further includes recombinant constructs comprising one or more of the sequences as broadly described above. The constructs may comprise a vector, such as a plasmid or viral vector, into which a sequence of the invention has been inserted, in a forward or reverse orientation. In a preferred aspect of this embodiment, the construct further comprises regulatory sequences, including, for example, a promoter, operably linked to the sequence. Large numbers of suitable vectors and promoters are known to those of skill in the art, and are commercially available. The following vectors are provided by way of example: Bacterial: pQE70, pQE60, pQE-9 (Qiagen), pBS, pD10, phagescript, psiX174, pbluescript SK, pbsks, pNH8A, pNH16a, pNH18A, pNH46A (Stratagene), ptrc99a, pKK223-3, pKK233-3, pDR540 and pRIT5 (Pharmacia); and Eukaryotic: pWLNEO, pSV2CAT, pOG44, pXT1, pSG (Stratagene) pSVK3, pBPV, pMSG, and pSVL (Pharmacia). However, any other suitable plasmid or vector may be used as long as it is replicable and viable in the host.

Promoter regions can be selected from any desired gene using CAT (chloramphenicol acetyl transferase) vectors or other vectors with selectable markers. Two appropriate vectors are pKK232-8 and pCM7. Particular named bacterial promoters include lacI, lacZ, T3, T7, gpt, lambda P.sub.R, P.sub.L and trp. Eukaryotic promoters include CMV immediate early, HSV thymidine kinase, early and late SV40,

LTRs from retrovirus, and mouse metallothionein-I. Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art.

Components of the expression vector may generally include: 1) a neomycin phosphotransferase (G418), or hygromycin B phosphotransferase (hyg) gene as a selection marker, 2) an E. coli origin of replication, 3) a T7 and SP6 phage promoter sequence, 4) lac operator sequences, 5) the lactose operon repressor gene (lacIq) and 6) a multiple cloning site linker region. Such an origin of replication (oriC) may be derived from pUC19 (LTI, Gaithersburg, Md.).

A nucleotide sequence encoding one of the polypeptides SEQ ID NOS:2,4 and 6 having the appropriate restriction sites is generated, for example, according to the PCR protocol described in Example 1 hereinafter, using PCR primers having restriction sites for KpnI (as the 5' primer) and NotI or SacI (as the 3' primer) for DPRP-1, or sites for HindIII (as the 5' primer) and NotI or BamHI (as the 3' primer) for DPRP-2. The PCR inserts are gel-purified and digested with compatible restriction enzymes. The insert and vector are ligated according to standard protocols.

In a further embodiment, the present invention provides host cells containing the above-described constructs. The host cell can be a higher eukaryotic cell, such as a mammalian cell, or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-Dextran mediated transfection, lipofection or electroporation (Davis, L., Dibner, M., Battey, I., Basic Methods in Molecular Biology, (1986)).

Such constructs in host cells are preferably used in a conventional manner to produce the gene product encoded by the recombinant sequence. Alternatively, the polypeptides of the invention can be synthetically produced by conventional peptide synthesizers or by chemical ligation of suitable fragments thus prepared.

Mature proteins can be expressed in mammalian cells, yeast, bacteria, or other cells under the control of appropriate promoters. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention. Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described by Sambrook, et al., Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor, N.Y., (1989), the disclosure of which is hereby incorporated by reference.

Transcription of the DNA encoding the polypeptides of the present invention by higher eukaryotes is increased by inserting an enhancer sequence into the vector.

Enhancers include cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Examples include the SV40 enhancer on the late side of the replication origin bp 100 to 270, a cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers.

Generally, recombinant expression vectors will include origins of replication and selectable markers permitting transformation of the host cell, e.g., the ampicillin-resistance gene of E. coli and S. cerevisiae TRP1 gene, and a promoter derived from a highly expressed gene to direct transcription of a downstream structural sequence. Such promoters can be derived from operons encoding glycolytic enzymes, such as 3-phosphoglycerate kinase (PGK), alpha-factor, acid phosphatase, or heat shock proteins, among others. The heterologous structural sequence is assembled in appropriate phase with translation initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein into the periplasmic space or extracellular medium. Optionally, the heterologous sequence can encode a fusion protein including an N-terminal identification peptide imparting desired characteristics, e.g., stabilization or simplified purification of expressed recombinant product.

Useful expression vectors for bacterial use are constructed by inserting a structural DNA sequence encoding a desired protein together with suitable translation initiation and termination signals in operable reading phase with a functional promoter. The vector will comprise one or more phenotypic selectable markers and an origin of replication to ensure maintenance of the vector and to, if desired, provide amplification within the host. Suitable prokaryotic hosts for transformation include *E. coli*, *Bacillus subtilis*, Salmonella typhimurium and various species within the genera Pseudomonas, Streptomyces, and Staphylococcus, although others may also be employed as a matter of choice.

As a representative but non-limiting example, useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and GEM1 (Promega Biotec, Madison, Wis., U.S.A.). These pBR322 "backbone" sections are combined with an appropriate promoter and the structural sequence to be expressed.

Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is induced by appropriate means (e.g.,

temperature shift or chemical induction), and cells are cultured for an additional period. Cells are typically harvested by centrifugation and then disrupted by physical or chemical means, with the resulting crude extract being retained for further purification. Microbial cells employed in expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption and use of cell-lysing agents; such methods are well known to those skilled in the art.

Various mammalian cell culture systems can also be employed to express a recombinant protein. Examples of mammalian expression systems include the COS-7 lines of monkey kidney fibroblasts, described by Gluzman, Cell, 23:175 (1981). Other cell lines capable of expressing a compatible vector include, for example, the C127, 3T3, CHO, HeLa and BHK cell lines. Mammalian expression vectors will generally comprise an origin of replication, a suitable promoter and enhancer, and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5' flanking nontranscribed sequences. DNA sequences derived from the SV40 splice, and polyadenylation sites may be used to provide required nontranscribed genetic elements.

The polypeptides can be recovered and purified from recombinant cell cultures by methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Recovery can be facilitated if the polypeptide is expressed at the surface of the cells, but such is not a prerequisite. Recovery may also be desirable of cleavage products that are cleaved following expression of a longer form of the polypeptide. Protein refolding steps as known in this art can be used, as necessary, to complete configuration of the mature protein. High performance liquid chromatography (HPLC) can be employed for final purification steps.

The polypeptides of the present invention may be purified natural products, or produced by recombinant techniques from a prokaryotic or eukaryotic host (for example, by bacterial, yeast, higher plant, insect or mammalian cells in culture). Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. Polypeptides of the invention may also include an initial methionine amino acid residue.

In a preferred embodiment, the proteins of the invention are isolated and purified so as to be substantially free of contamination from other proteins. For example, the proteins of the invention should constitute at least 80% by weight of the total protein

present in a sample, more preferably at least 90%, even more preferably at least 95%, and most preferably at least 98% by weight of the total protein.

These proteins may be in the form of a solution in water, another suitable solvent, such as dimethyl sulphoxide (DMSO) or ethanol, or a mixture of suitable solvents. Examples of mixtures of solvents include 10% (by weight) ethanol in water and 2% (by weight) DMSO in water. A solution may further comprise salts, buffering agents, chaotropic agents, detergents, preservatives and the like. Alternatively, the proteins may be in the form of a solid, such as a lyophilised powder or a crystalline solid, which may also comprise a residual solvent, a salt or the like.

As used herein, the term "antibodies" includes polyclonal antibodies, affinity-purified polyclonal antibodies, monoclonal antibodies, and antigen-binding fragments, such as $F(ab')_2$ and Fab' proteolytic fragments. Genetically engineered intact antibodies or fragments, such as chimeric antibodies, Fv fragments, single chain antibodies and the like, as well as synthetic antigen-binding peptides and polypeptides, are also included. Non-human antibodies may be humanized by grafting non-human CDRs onto human framework and constant regions, or by incorporating the entire non-human variable domains (optionally "cloaking" them with a human-like surface by replacement of exposed residues, wherein the result is a "veneered" antibody). In some instances, humanized antibodies may retain non-human residues within the human variable region framework domains to enhance proper binding characteristics. Through humanizing antibodies, biological half-life may be increased, and the potential for adverse immune reactions upon administration to humans should be reduced.

Alternative techniques for generating or selecting antibodies useful herein include in vitro exposure of lymphocytes to human prohormone DPRP protein or a peptide therefrom, and selection of antibody display libraries in phage or similar vectors (for instance, through use of immobilized or labeled human DPRP protein or peptide). Genes encoding polypeptides having potential human DPRP polypeptide binding domains can be obtained by screening random peptide libraries displayed on phage (phage display) or on bacteria, such as *E. coli*. Nucleotide sequences encoding such polypeptides can be obtained in a number of ways well known in this art.

As would be evident to one of ordinary skill in the art, polyclonal antibodies can be generated from inoculating a variety of warm-blooded animals, such as horses, cows, goats, sheep, dogs, chickens, rabbits, mice and rats, with a human DPRP polypeptide or a fragment thereof. The immunogenicity of a human prohormone DPRP polypeptide may be increased through the use of an adjuvant, such as alum (aluminum hydroxide) or

Freund's complete or incomplete adjuvant, or surface active substances, such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH or dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable. Polypeptides useful for immunization also include fusion polypeptides, such as fusions of DPRP or a portion thereof with an immunoglobulin polypeptide or with maltose binding protein. The polypeptide immunogen may be a full-length molecule or a portion thereof. If the polypeptide portion is "hapten-like", such portion may be advantageously joined or linked to a macromolecular carrier, such as keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA) or tetanus toxoid, for immunization. Antibodies to DPRP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which block or modify interactions at the active sites) are especially preferred for therapeutic use.

For the production of antibodies, binding proteins, or peptides which bind specifically to DPRP, libraries of single chain antibodies, Fab fragments, other antibody fragments, non-antibody protein domains, or peptides may be screened. The libraries could be generated using phage display, other recombinant DNA methods, or peptide synthesis (Vaughan, T. J. et al. Nature Biotechnology 14: 309-314 (1966)). Such libraries would commonly be screened using methods which are well known in the art to identify sequences which demonstrate specific binding to DPRP.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to DPRP have an amino acid sequence consisting of at least about 5 amino acids and, more preferably, of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein. Short stretches of DPRP amino acids may also be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to DPRP may be prepared using any well known technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique, although monoclonal antibodies produced by hybridoma cells may be preferred.

In addition, techniques developed for the production of "chimeric antibodies", such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used, see Neuberger, M.S. et al. Nature 312: 604-608 (1984). Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce DPRP-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (Burton D. R. Proc. Natl. Acad. Sci. 88: 11120-11123 (1991)).

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (Orlandi, R. et al. Proc. Natl. Acad. Sci. 86: 3833-3837 (1989)).

Antibody fragments which contain specific binding sites for DPRP may also be generated. For example, such fragments include, but are not limited to, $F(ab')_2$ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (Huse, W. D. et al. Science 254: 1275-1281 (1989)).

Various immunoassays may be used to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between DPRP and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering DPRP epitopes is preferred, but a competitive binding assay may also be employed.

As earlier mentioned, the DPRPs can be used in treatment of the Diseases. Pharmaceutical compositions suitable for use in this aspect of the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose relating to one of the Diseases. The determination of a therapeutically effective dose is well within the capability of those skilled in the art and can be estimated initially either in cell culture assays, e.g. of neoplastic cells, or in animal models, usually mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration, which

information is then commonly used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, e.g. a DPRP or fragment thereof, antibodies of DPRP, or an agonist, antagonist or inhibitor of DPRP, which ameliorates particular symptoms or conditions of the Disease. For example, the amount to be administered may be effective to cleave a desired target substrate upon contact therewith. Therapeutic efficacy and toxicity may likewise be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED50 (the dose therapeutically effective in 50% of the population) or LD50 (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, and it can be expressed as the LD50/ED50 ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies is used in formulating a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

An exact dosage will normally be determined by the medical practitioner in light of factors related to the subject requiring treatment, with dosage and administration being adjusted to provide a sufficient level of the active moiety or to maintain a desired effect. Factors to be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or even once every two weeks, depending on the half-life and clearance rate of the particular formulation.

Yet another aspect of the invention provides polynucleotide molecules having sequences that are antisense to mRNA transcripts of DPRP1, DPRP2 and DPRP-3 polynucleotides. Administration of an antisense polynucleotide molecule can block the production of the protein encoded by DPRP-1, DPRP2 or DPRP-3. The techniques for preparing antisense polynucleotide molecules and administering such molecules are known in the art. For example, antisense polynucleotide molecules can be encapsulated into liposomes for fusion with cells.

In particular, the expression of DPRP-1, DPRP-2 and DPRP-3 in specialized epithelial cells, immune cells (lymphocytes and B cells), astrocytic tumors, and in

various hormone sensitive cancers provides evidence of a potential role in the pathophysiology of cancer, metaplasia and metastasis. Therefore in a further aspect, the invention relates to diagnostic assays for detecting diseases associated with inappropriate DPRP activity or expression levels. Antibodies that specifically bind DPRP may be used for the diagnosis of disorders characterized by expression of DPRP, or in assays to monitor patients being treated with DPRP or with agonists or antagonists (inhibitors) of DPRP. Antibodies useful for diagnostic purposes may be prepared in the same manner as those described above for therapeutics. Diagnostic assays for DPRP include methods that utilize the antibody and a label to detect DPRP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and they may be labeled by covalent or non-covalent joining with a reporter molecule. A wide variety of reporter molecules are known in the art. Recombinant DPRP proteins that have been modified so as to be catalytically inactive can also be used as dominant negative inhibitors. Such modifications include, for example, mutation of the active site.

A variety of protocols for measuring DPRP, including ELISAs, RIAs and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of DPRP expression. Normal or standard values for DPRP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to DPRP under conditions suitable for complex formation. The method for detecting DPRP in a biological sample would comprise the steps of: a) providing a biological sample; b) combining the biological sample and an anti-DPRP antibody under conditions which are suitable for complex formation to occur between DPRP and the antibody; and c) detecting complex formation between DPRP and the antibody, thereby establishing the presence of DPRP in the biological sample. The amount of complex formation then may be quantified by various methods, preferably by photometric means. Quantities of DPRP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding DPRP are used for diagnostic purposes, which polynucleotides may include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. These polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which expression of DPRP may be correlated with one of the Diseases. The diagnostic assay may be used to distinguish between absence, presence, and excess expression of DPRP and to monitor regulation of DPRP levels during therapeutic

intervention. Moreover, pharmacogenomic, single nucleotide polymorphisms (SNP) analysis of the DPRP genes can be used as a method to screen for mutations that indicate predisposition to disease or modified response to drugs.

DPRP polynucleotide and polypeptide sequences, fragments thereof, antibodies of DPRPs, and agonists, antagonists or inhibitors of DPRPs can be used to as discovery tools to identify molecular recognition events and therefore proteins, polypeptides and peptides that interact with DPRP proteins. A specific example is phage display peptide libraries where greater than 108 peptide sequences can be screened in a single round of panning. Such methods as well as others are known within the art and can be utilized to identify compounds that inhibit or enhance DPRP-1, DPRP-2 or DPRP-3 activity. Coupled links represent functional interactions such as complexes or pathways, and proteins that interact with DPRPs can be identified by a yeast two-hybrid system, proteomics (differential 2D gel analysis and mass spectrometry) and genomics (differential gene expression by microarray or serial analysis of gene expression SAGE). Proteins identified as functionally linked to DPRPs and the process of interaction form the basis of methods of screening for inhibitors, agonists and antagonists and modulators of these DPRP-protein interactions.

The term "antagonist," as it is used herein, refers to an inhibitor molecule which, when bound to DPRP, decreases the amount or the duration of the effect of the biological or immunological activity of DPRP, e.g. decreasing the enzymatic activity of the peptidase to cleave the N-terminal dipeptide. Antagonists may include proteins, nucleic acids, carbohydrates, antibodies, or any other molecules which decrease the effect of DPRP; for example, they may include small molecules and organic compounds that bind to and inactivate DPRPs by a competitive or non-competitive type mechanism. Specific examples of DPRP tetrapeptide peptidic enzyme activity inhibitors are described in Example 6 and 7. Inhibitors can be, for example, inhibitors of the DPRP protease activity, or alternatively inhibitors of the binding activity of the DPRP to proteins with which they interact. Specific examples of such inhibitors can include, for example, anti-DPRP antibodies, peptides, protein fragments, or small peptidyl protease inhibitors, or small non-peptide, organic molecule inhibitors which are formulated in a medium that allows introduction into the desired cell type. Alternatively, such inhibitors can be attached to targeting ligands for introduction by cell-mediated endocytosis and other receptor mediated events. Such methods are described further below and can be practiced by those skilled in the art given the DPRP nucleotide and amino acid sequences described herein.

A further use for DPRPs is for the screening of potential antagonists for use as therapeutic agents, for example, for inhibiting binding to DPRP, as well as for screening for agonists. DPRP, its immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds which are prospective agonists or antagonists in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between DPRP and the agent being tested is then measured. Other assays to discover antagonists that will inhibit DPRP are apparent from the disclosures of U.S. Patents Nos. 6,011,155, 6,107,317, 6,110,949, 6,124,305 and 6,166,063, which describe inhibitors of DPPIV. Another worthwhile use of these DPRPs is the screening of inhibitors of DPPIV to show that they will not have undesired side effects by also inhibiting one or more of the DPRPs.

A method provided for screening a library of small molecules to identify a molecule which binds DPRP generally comprises: a) providing a library of small molecules; b) combining the library of small molecules with the polypeptide of either SEQ ID NOS:1, 3 or 5, or with a fragment thereof, under conditions which are suitable for complex formation; and c) detecting complex formation, wherein the presence of such a complex identifies a small molecule which binds DPRP.

One method for identifying an antagonist comprises delivering a small molecule which binds DPRP into extracts from cells transformed with a vector expressing DPRP along with a chromogenic substrate (e.g. Ala-Pro-AFC or Ala-Pro-AMC) under conditions where cleavage would normally occur, and then assaying for inhibition of cleavage by the enzyme by monitoring changes in fluorescence, or UV light absorption, by spectrophotometry to identify molecules that inhibit cleavage. A reduced rate of reaction or total amount of fluorescence or UV light absorption, in the presence of the molecule, establishes that the small molecule is an antagonist which reduces DPRP catalytic/enzymatic activity. Once such molecules are identified, they may be administered to reduce or inhibit cleaving by a DPRP.

The term "agonist," as used herein, refers to a molecule which, when bound to DPRP, increases or prolongs the duration of the effect of DPRP. Agonists may include proteins, nucleic acids, carbohydrates, or any other molecules that bind to and modulate the effect of DPRP. Although it is less likely that small molecules will prove to be effective DPRP agonists, a method for identifying such a small molecule, which binds DPRP as an agonist, comprises delivering a chromogenic form of a small molecule that binds DPRP into cells transformed with a vector expressing DPRP and assaying for

fluorescence or UV light absorption changes by spectrophotometry. An increased amount of UV absorption or fluorescence would establish that the small molecule is an agonist that increases DPRP activity.

Another technique for drug screening which may be used provides for high throughput screening of compounds having suitable binding affinity to the protein of interest as described in published PCT application WO84/03564. In this method, large numbers of different small test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The test compounds are reacted with DPRP, or with fragments thereof, and then washed. Bound DPRP is then detected by methods well known in the art. Purified DPRP can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding DPRP specifically compete with a test compound for binding DPRP. In this manner, antibodies can be used to detect the presence of any peptide that shares one or more antigenic determinants with DPRP.

As indicated above, by investigating the binding sites, ligands may be designed that, for example, have more interactions with DPRP than do its natural ligands. Such antagonist ligands will bind to DPRP with higher affinity and so function as competitive ligands. Alternatively, synthetic or recombinant proteins homologous or analogous to the ligand binding site of native DPRP may be designed, as may other molecules having high affinity for DPRP. Such molecules should also be capable of displacing DPRP and provide a protective effect.

As indicated above, the knowledge of the structures of DPRP enables synthetic binding site homologues and analogues to be designed. Such molecules will facilitate greatly the use of the binding properties to target potential therapeutic agents, and they may also be used to screen potential therapeutic agents. Furthermore, they may be used as immunogens in the production of monoclonal antibodies, which antibodies may themselves be used in diagnosis and/or therapy as described hereinbefore.

Given the ubiquitous expression of several members of the prolyl oligopeptidase S9B family, cell lines in which targeted gene disruption of DPPIV, DPRP-1, DPRP-2, DPRP-3, FAP and DPPVI to establish the null phenotype will be of great value to assist screening for selective and potent compounds. Accordingly, the invention provides such cell lines engineered with Lox-Neo IRES tk cassette and GFP-IRES-Neo Knock-in/out cassette DNA element for constructing somatic gene targeting vectors.

Example 1

Cloning and Expression of DPRP genes Using the Mammalian Expression System

DNA fragments encoding the full-length polypeptide DPRP-1 were amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene, i.e. SEQ ID NO:45 and NO:46. In addition, DNA fragments encoding the full length polypeptide DPRP-2 were amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of that gene, i.e. SEQ ID NO:50 and NO:51. Furthermore, DNA fragments encoding the full length polypeptide DPRP-3 were amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of that gene, i.e. SEQ ID NO:55 and NO:56.

The three amplified sequences were respectively isolated from a 0.7% agarose gel using commercially available kit (GFX PCR DNA and Gel Band Purification Kit, Amersham Pharmacia Biotech Inc., Piscataway NJ, USA). The fragments were then ligated into cloning vector, pGEM-7Zf(-) (Promega Corporation, Madison WI, USA) and sequenced. The corresponding cloning constructs were respectively designated pGEM7-DPRP1, pGEM7-DPRP2 and pGEM7-DPRP3. The DNA sequences encoding the truncated DPRP-1 or DPRP-2 or DPRP-3 were amplified using pGEM7-DPRP1 or pGEM7-DPRP2 or pGEM7-DPRP3 as a template and PCR oligonucleotide primers. SEQ ID NO:45 and NO:47 were used for DPRP-1; SEQ ID NO:50 and NO:52 were used for DPRP-2; and SEQ ID NO:57 and NO:58 for DPRP-3. The amplified sequences were again isolated from a 0.7% agarose gel using the same purification kits and sub-cloned into pGEM-7Zf(-). The resulting constructs were designated pGEM7-DPRP1f, pGEM7-DPRP2f and pGEM7-DPRP3f.

To make the DPRP-1 mammalian expression construct, pGEM7-DPRP1 was digested with the restriction enzymes KpnI and NotI to release the full length DPRP-1 gene. The DNA fragment carrying the DPRP-1 gene was gel band purified using the above kit and then inserted into expression vector pcDNA3 (Invitrogen, Carlsbad CA, USA) to make the native DPRP-1 expression construct, which was designated pcDNA-DPRP1. pGEM7-DPRP1f was digested with the restriction enzymes XbaI and HindIII to release the truncated DPRP-1f gene. The DNA fragment carrying the DPRP-1f gene was gel band purified using the above kit and then inserted into expression vector pcDNA3.1(-)/myc-His A (Invitrogen, Carlsbad CA, USA) to make the tagged DPRP-1 expression construct pcDNA-MycHis-DPRP1.

To make the DPRP-2 mammalian expression construct, pGEM7-DPRP2 was digested with the restriction enzymes HindIII and BamHI to release the full length DPRP-2 gene. The DNA fragment carrying the DPRP-2 gene was gel band purified using the above kit and then inserted into expression vector pcDNA3 (Invitrogen, Carlsbad CA, USA) to make the native DPRP-2 expression construct, which was designated pcDNA-DPRP2. pGEM7-DPRP2f was digested with the restriction enzymes EcoRI and BamHI to release the truncated DPRP-2f gene. The DNA fragment carrying the DPRP-2f gene was gel band purified using the above kit and then inserted into expression vector pcDNA3.1(-)/myc-His B (Invitrogen, Carlsbad CA, USA) to make the tagged DPRP-2 expression construct designated pcDNA-MycHis-DPRP2.

To make the DPRP-3 mammalian expression construct, pGEM7-DPRP3 was digested with the restriction enzymes EcoRI and XhoI to release the full length DPRP-3 gene. The DNA fragment carrying the DPRP-3 gene was gel band purified using the above kit and then inserted into expression vector pcDNA3 (Invitrogen, Carlsbad CA, USA) to make the native DPRP-3 expression construct designated pcDNA-DPRP3. pGEM7-DPRP3f was digested with the restriction enzymes NheI and ApaI to release the truncated DPRP-3f gene. The DNA fragment carrying the DPRP-3f gene was gel band purified using the above kit and then inserted into expression vector pcDNA3.1(-)/myc-His B (Invitrogen, Carlsbad CA, USA) to make the tagged DPRP-3 expression construct pcDNA-MycHis-DPRP3.

Example 2

Expression Pattern of DPRP genes in human tissues

Quantitative PCR analysis was carried out to examine the levels of expression of the mRNAs for the polypeptides of the present invention in human tissues. RT PCR was also carried out on a number of human cell lines including but not limited to prostate cancer cells (LNCaP, PC3, DU145), the MLTC-1 line (mouse testis), and MDA-MB231 cells (breast cancer). Bands of the expected sizes for DPRP-1, DPRP-2 and DPPIV were all expressed in the various cancer cells lines, with FAP also being expressed at very low levels.

Northern Blot Analysis

Northern blot analysis was performed with 2µg poly(A)$^+$ RNA isolated from eight different tissues using DPRP probes. Specifically, a human Multiple Tissue Northern (MTN) blot (Clontech, Palo Alto, Calif.) was probed with a 1 kb N-terminal fragment that had been radioactively labeled by random priming in the presence of a

^{32}PdCTP (A. P. Feinberg et al., Anal. Biochem., 132, 6 (1983)). Hybridization was performed at 68°C overnight in ExpressHyb™ hybridization solution (Clontech, Palo Alto, Calif.). The blots were first washed at room temperature in 2 times SSC and 0.05% SDS, and then washed at 60°C (DPRP-1 & DPRP-2) and 50°C (DPRP-3) in 0.1 times SSC and 0.1% SDS.

Northern analysis showed expression of DPRP-1 in several tissues with the most abundant signal being in testis, prostate, muscle and brain. Testis showed 3 transcripts approximately 7.5, 4.5 and 2.5 kb in length. The shorter mRNA species was very abundant in testis but negligible in the other tissues tested. DPRP-2 was ubiquitously expressed in every tissue with highest levels in liver and muscle and a predominant transcript at 5kb. DPRP-3 expression was limited to brain and pancreas. Further analysis was conducted for the three proteases in specific brain regions (cerebellum, cortex, medulla, spinal cord, occipital lobe, frontal lobe temporal lobe and putamen). DPRP-1 was expressed in all regions with low levels present in the spinal cord, while DPRP-2 was expressed in all brain regions tested.

Oligonucleotide primers SEQ ID NO:48 and NO:49 were used for DPRP-1 quantitative PCR, whereas oligonucleotide primers SEQ ID NO:53 and NO:54 were used for DPRP-2 quantitative PCR. Human Multiple Tissue cDNA (MTC™) Panel I and Panel II (Clontech, Palo Alto CA, USA) were used as normalized cDNA templates. 0.5 ng of each cDNA were used in a 25 µl PCR reaction, with each primer at a final concentration of 300 nM. The PCR reaction was performed using a SYBR Green PCR Core Reagents Kit (Applied Biosystems, Foster City CA, USA) and detected with an Applied Biosystems GeneAmp 5700 sequence detection system. Manufacturer's recommended thermal cycling parameter, e.g. 50°C for 2 min, 95°C for 10 min followed by 40 cycles of 95°C for 15 sec and 60°C for 1 min was used. Data obtained shows relatively high rates of expression for both DPRP-1 and DPRP-2 in the pancreas, ovary and testis, and a particularly high rate for DPRP-2 in the liver.

Example 3 – Production of DPRP Polyclonal Antibodies and Western Blotting

The amino acid sequence deduced from the cDNA encoding DPRP-1 was analyzed using DNASTAR software (DNASTAR, Inc.) to determine regions of high immunogenicity, and a corresponding oligopeptide was synthesized and used to raise anti-DPRP-1 antibodies. The procedure was repeated for DPRP-2 and DPRP-3. The selection of appropriate peptide sequences and the techniques for antibody production

are methods well known to those of skill in the art. Selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions, is well known in this art.

Typically, oligopeptides that are about 15 to 20 residues in length, e.g. SEQ ID NO:59 for DPRP-1, SEQ ID NO:60 for DPRP-2 and SEQ ID NO:61 for DPRP-3, were synthesized using an Applied Biosystems Peptide Synthesizer Model 431 A. Fmoc-chemistry was used and the 19- or 15-residue peptides were respectively coupled to keyhole limpet hemocyanin (KLH, Sigma, St. Louis, Mo.) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS). Rabbits were immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. The resulting antisera were tested for antipeptide activity, e.g., by binding the peptide to plastic, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radioiodinated, goat anti-rabbit IgG.

Western blotting was performed using normal human protein samples (Protein Medley) obtained from Clontech (about 36 μg of total proteins). Proteins were fractionated through 10% SDS-polyacrylamide gels, and transferred to 0.45 mm nitrocellulose membranes. Membranes were blocked in Tris-buffered saline (TBS) with 0.05% Tween 20 and 1% BSA. Anti DPRP-1 or DPRP-2 specific antibodies were used as primary antibodies and were diluted 1:5,000 in Tris-buffered saline with 0.05% Tween 20 (TBST) and the Alkaline Phosphatase (AP) conjugated goat anti-Rabbit IgG (Promega) was diluted 1: 5,000 in the same buffer before use. The positive reaction was visualized by incubating the membrane in Western Blue Stabilized Substrate (Promega) for AP until the bands of interest have reached the desired intensity. DPRP-1 and DPRP-2 proteins were detected in brain, muscles, kidney, prostate, testis and ovary tissues. DPRP-1 and DPRP-2 were synthesized as approximately 101kDa and 100kDa forms, respectively, which are in good agreement with the molecular masses estimated from their primary structure as shown in Table 3.

Table 3. Predicted Molecular Weight, Number of potential N-linked glycosylation sites (Asn residues) and predicted pI values of DPRP-1, DPRP-2 and DPRP-3, based on sequence analysis using the method developed by Hopp and Woods, Proc. Nat. Acad. Sci. 78:3824-3828 (1981).

	M.W. (Da.)	No. of Asn	pI
DPRP1	101422	26	5.39
DPRP2	98263	27	6.01
DPRP3	90914	33	6.11

Several additional bands of similar molecular weight were observed. These are thought to be due to the presence of post-translational glycosylation of the proteins. Table 3 also shows the number of potential N-glycosylation sites for the DPRP proteins. The presence of glycosylated and unglcosylated forms of the proteins was evaluated using tunicamycin, an inhibitor of the oligosaccharide synthesis. It is evident that the smaller forms were unglycosylated forms. The correlation between mRNA (Northern analysis) and protein quantity (Western analysis) for DPRP-1 is shown in Table 4.

Table 4. Correlation of mRNA and protein expression of DPRP-1 in human tissues

	Heart	Brain	Placenta	Muscles	Kidney	Prostate	Testis	Ovary
Northern	++	+++	+	+++	++	+++	++++	+
Western	-	++++	-	+	++	+	+++	+++

Example 4

Immunohistochemical localization of DPRP proteins in human tissues

Four-micron sections were prepared from a number of different formalin-fixed, paraffin-embedded human tissues. Tissue sections were deparaffined through 4 immersions in xylenes for 5 minutes, followed by a graded alcohol series to distilled water. Steam heat induced epitope recovery (SHIER) was used with several different SHIER solutions with and without enzyme digestion tissue in two different concentrations (Ladner et al, Cancer Res.; 60, p 3493-3503, 2000). The treatments and antibody dilutions employed are outlined below.

1. Blocking Reagent for 15 minutes (Normal Goat Serum)
2. Primary Antibody for 25, 60 min or overnight incubation
3. Secondary Antibody for 25 minutes (Biotinylated Goat-anti-rabbit IgG)
4. Endogenous Peroxidase Blocking for 3 x 1.5 minutes
5. ABC (avidin-biotin complex) / Horse Radish Peroxidase for 25 minutes
6. DAB Chromogen for 3 x 5 minutes (Brown reaction product)
7. Light Hematoxylin Counter Stain 1 minute

Positive controls were run to assure the detection chemistries and antigen pretreatments were working appropriately. Rabbit IgG was run as a negative control. An avidin-biotin based tissue staining system was used for the detection of the DPRP-1 antibody. Horseradish peroxide was used as a reporter enzyme with DAB as chromogen.

After staining, slides were dehydrated through an alcohol series to absolute ethanol followed by xylene rinses. Slides were permanently coverslipped with glass coverslips and permount. Digital images of representative staining, where positive staining was indicated by a dark brown chromogen (DAB-HRP reaction product), were captured using a video camera from Olympus. Hematoxylin counterstain provides a blue nuclear stain to assess cell and tissue morphology.

DPRP-1 rabbit polyclonal antibody labels formalin-fixed, paraffin-embedded human tissues, including normal testis, prostate glands, endometrial glands, tonsils and pancreas. It was also present in endothelial cells of normal ovary, bladder and kidney. Staining was localized in the cytoplasm in epithelial and some stromal cells such as fibroblasts, endothelial cells and lymphocytes. Interestingly in normal testis tested with DPRP-1 antibodies, there was distinctive expression in Leydig cells and multinucleated macrophages found in interstitial tissue, which is the space surrounding the seminiferous tubules. Tonsil B cells were stained with DPRP-1 antibody.

Example 5

Mammalian and Insect Cell Expression of DPRP Proteins and Purification

Plasmid DNA of pcDNA-DPRP1, pcDNA-MycHis-DPRP1, pcDNA-DPRP-2 or pcDNA-MycHis-DPRP2 was transfected into PEAK (EdgeBioSystems, Gaithersburg MD, USA) or COS-1 (ATCC CRL-1650) using LipofectAmine (Life Technologies, Gaithersburg MD, USA) method recommended by the manufacturer. Transfected cells were maintained in DMEM with 5% FBS at 37°C with 5% CO_2 for 48 hours. Cells were then collected and used for recombinant protein extraction. Cells were harvested 48 hours after transfection, homogenized and then spun at 18,000 x g for 40 min. The supernata were collected as cytosolic fractions. This fraction was loaded on TALON spin column (Clontech), and His-tagged proteins were eluted with 50mM PBS, 150mM imidazole, pH 7. Recombinant proteins were then detected by western blotting with anti-myc antibody and visualized using a ProtoBlot II AP system (Promega). Recombinant affinity purified fusions of the DPRP-1 and DPRP-2 were detected by western blot, and DPRP-1 and DPRP-2 were synthesized as 112kDa and 109kDa forms as predicted.

Naturally occurring or recombinant DPRP proteins were substantially purified by immunoaffinity chromatography using antibodies specific for DPRP-1, DPRP-2 or DPRP-3. An immunoaffinity column was constructed by covalently coupling DPRP antibodies to an activated chromatographic resin, such as CNBr-activated Sepharose

(Pharmacia & Upjohn). After the coupling, the resin was blocked and washed according to the manufacturer's instructions.

Media or cell extracts containing DPRP proteins were passed over the immunoaffinity column, and the column was washed under conditions that allow the preferential absorbance of DPRPs (e.g., high ionic strength buffers in the presence of detergent). The column was eluted under conditions that disrupt antibody/DPRP binding (e.g., a buffer of pH 2-3 or a high concentration of a chaotrope, such as urea or thiocyanate ion), and purified DPRP was collected.

Example 6

Enzymatic Activity of DPRP proteins and Methods of Screening for Inhibitors

The kinetic properties of recombinant DPRP-1 and DPRP-2 were determined in a continuous fluorimetric assay. Buffer, pH and temperature dependence optimization led to the following assay conditions: Enzyme assays were performed in 50mM PBS, pH7.4 50 µl (50 µg/ml) of purified enzymes were mixed with 1 µl of different concentration of Ala-Pro-AMC (Enzyme Systems). Plates were then incubated at 37°C for 30 min, and fluorescence was detected using a Wallac 1420 Fluorimeter with λex40355 and λem535. The K_m values of DPRP-1 and DPRP-2 were similar (208 and 161 µM respectively).

Further biochemical characterization reveals that DPRP-1 and DPRP-2 have similar profiles to DPPIV. The two purified proteases and DPPIV were preincubated with inhibitors at room temperature for 30 min. Substrate, Ala-Pro-AMC (100 µM), was then added, and the fluorescence intensity was recorded as 60 readings during a 60 min period. The irreversible serine protease inhibitor AEBSF was the only inhibitor tested that showed strong inhibition of all three enzymes (Table 5). This confirms the structural and domain analysis prediction that these proteins belong to the serine protease superfamily.

Table 5. Inhibition of DPRP-1 and DPRP-2 by Protease Inhibitors

Inhibitor	Inhibitor Property	Concentration	Residual activity (% of control)		
			DPRP-1	DPRP-2	DPPIV
AEBSF	serine, irreversible	5mM	29.6	23.9	21.1
Aprotinin	serine, reversible	5µg/ml	77.5	63.2	80.2
Pepstatin	aspartic, reversible	2µg/ml	97.3	95.0	93.5
DTT	cysteine	2mM	100.1	94.8	98.3
B-Mercaptoethonal	cysteine	100mM	93.2	84.0	98.0
EDTA	metallo, reversible	2mM	91.5	86.0	93.5
Leupeptin	serine, reversible	50µg/ml	91.1	90.4	90.7

In addition to Ala-Pro-AMC, additional substrates tested also confirmed that DPRP-1 and DPRP-2 are dipeptidyl peptidases. The data were derived by determining the fluorescence change following a 30-minute incubation of the substrates (125 µM) with enzymes as a percentage of the fluorescence measured at Ala-Pro-AMC and Gly-Pro-AMC were the only good substrates among those tested.

Table 6. DPRP-1 and DPRP-2 are dipeptidyl peptidases.

Substrate	% Change in Fluorescence at 30 minutes		
	DPRP-1	DPRP-2	DPPIV
Ala-Pro-AMC	239.0	127.5	379.0
Gly-Pro-AMC	341.5	205.0	444.0
Ala-Pro-pNA	45.5	44.0	29.5
Pro-pNA	-1	-2.5	0.0
Gly-Arg-pNA	-4.5	-0.5	0.0
Lys-Ala-pNA	2.5	0.5	0.5
Ala-Phe-Pro-pNA	-4	-0.5	2.0

Additional natural and non-natural amino acid di-, tri- and tetra-peptides were tested in order to find an optimal substrate for testing each of the DPRP proteins that will also show reduced activity when incubated DPPIV.

The enzyme assay method described here is one of a number of methods that can be utilized to screen for peptide and non-peptide inhibitors of the DPRP enzymes. Libraries of tetrapeptide inhibitors were tested to discover inhibitors of enzyme activity. Candidate inhibitors were prepared as 10-20 mM stock solutions in DMSO and stored at -20°C. Dilutions were made in assay buffer. Inhibition was determined by comparing

the changes in fluorescence of the inhibited enzyme to the change in fluorescence of the control (vehicle) enzyme. 100-(fl units of sample/fl units of control x 100) gives percent inhibition value. The percent inhibition and the inhibitor concentration at which the enzyme was 50% inhibited (IC_{50}) was ascertained by plotting percent inhibition vs. inhibitor concentration on the log scale. As shown in Figure 3, several tetrapeptides amides inhibited enzyme activity, wherein data are expressed as the % of activity in the presence of vehicle (0.02% DMSO) alone. Compounds were added at 1 mM. Most interesting was the apparent differential activity of some tetrapeptides for DPRP-1 and DPRP-2, compared to DPPIV. While all three enzymes were inhibited by Peptide-1, only DPRP-1 and DPRP-2 were significantly inhibited by Peptide-4 and Peptide-5. This demonstrates that selective inhibition of the purified enzymes is achievable.

The assay described in this example can also be used to screen additional synthetic or naturally occurring compound libraries, including macromolecules, for agents that either inhibit or enhance DPRP activity. The DPRP-1 and DPRP-2 polypeptides to be used in the assay can be obtained by, for example, *in vitro* translation, recombinant expression (see Example 5) or biochemical procedures. Methods other than those described here can also be used to screen and identify compounds that inhibit DPRP-1, DPRP-2 or DPRP-3, which methods can include, for example, binding assays such as ELISAs and RIAs.

Example 7

Effect of DPRP Inhibitors on the Proliferation of Human Cancer Cells In Vitro

In an attempt to assess the effect that several inhibitors of DPRP-1 and DPRP-2 activity may have on the proliferation of human cancer cells, LNCap, PC3 and Du145, mouse testis line MLTC-1 and MDA-MB231 breast cancer cells were plated (10^4 per well) in 96-well tissue culture plates and allowed to grow and attach for 24 hours at 37°C in a CO_2 incubator. Compounds at various dilutions (final dilutions: 0.1 nM – 10 μM) were then added to the wells for various incubation periods from 24 hours to 96 hours, with fresh compound being replaced each day. Addition of the diluent DMSO alone served as the control. Following incubation with these compounds in triplicate, proliferation of the cells was determined using an XTT cell proliferation assay (Roche 1-465-015). The plates were read at 490 and 650nm 5 hours after the XTT mix was added. An increase in cell proliferation was observed with three of the inhibitors at concentrations equal to 0.1, 1, 10 and 100 x IC_{50}, and the results are shown in FIGS. 4A, 4B and 4C for PC3 cells.

Overall, the DPRPs are expressed in a wide variety of tissues as has been demonstrated by mRNA amplification, western blotting and immunohistochemistry. DPRP-1 was most abundant in the testis by Northern blot and western blot. The large number of expressed sequence tags (ESTs) from testis cDNA sources that are homologous to DPRP-1 also confirms abundant expression of DPRP-1 in testis. Example 4 describes the immunohistochemical localization of DPRP-1 protein in human testis using a specific DPRP-1 antibody. DPRP-1 is strongly expressed in epitheloid Leydig cells, and Leydig cells are the primary source of testicular androgens (male steroid hormones) in the mammalian male. In the interstitium of the testis, Leydig cells and macrophages are in close association with "digitation" of Leydig cell process extending onto macrophage surface. Multinucleated cells in close proximity to the Leydig cells were also stained with DPRP-1 antibody suggesting that the protease was also expressed in macrophages, and macrophages in the testis play an important role in the paracrine regulation of Leydig cells. Cytokines secreted by the testicular macrophages are mitogenic to Leydig cells and play an important role in the differentiation of mesenchymal progenitor cell into mature Leydig cells. A clearer understanding of the proteins and pathways involved in the maturation of the testis is important for the discovery of new treatments for precocious puberty. In addition, Leydig cells cause tumors such as sex cord-stromal tumors via sexual steroid production (predominantly testosterone). Testosterone is associated with several neoplasia and diseases such as breast carcinoma and uterine cancers, ovarian carcinoma and androgenic alopecia (hair loss). Further examination of the localization of DPRP proteins in other glands in the body (e.g. adrenal glands) that produce testosterone and other androgenic hormones are currently under investigation. The possible association of DPRP-1 with steroid and polypeptide hormone biosynthetic pathways functions is being investigated, and Example 7 is relevant to understanding the role of DPRP proteins in prostate, testis and breast in vitro cell models.

Immunohistochemical analysis also localized DPRP-1 to endometrial glands in the uterus (see Example 4), pancreatic acini, glomeruli of the kidney, plasma cells in the bladder, a subset of B-cells in the tonsils, columnar epithelial cells of the prostate and poorly differentiated prostate squamous metaplasia, Gleason grade 4 prostatic carcinoma, and hyperplastic glands in benign prostatic hyperplasia. Positive staining in breast carcinoma, as well as in seminoma and prostate squamous metaplasia, suggests a general association of DPRP-1 with hormone-sensitive tissues, particularly in cells that become poorly differentiated. The presence of the DPRP-1 in specialized epithelial cells

and in inflammatory plasma cells (lymphocytes) is also of interest. Inflammatory breast carcinoma has an abundance of infiltrating lymphocytes and an overall bad prognosis. DPRP-1 and other DPRP proteins appear in medullary carcinomas that typically have a constant infiltrating lymphoplasmacytic component at the periphery of the tumor, which is thought to represent a reaction of the host tissues to the neoplasm. Most of the lymphocytes are T Cells, and most of the plasma cells are of the IgG-producing type. Several antigens are abundant on B cells, a subgroup of breast-cancer cells, and other epithelial cancer cells, and these antigens are targets for a new class of therapeutic monoclonal antibodies with some notable success having been achieved with a humanized monoclonal antibody against the B-cell–specific antigen CD20. Accordingly, monoclonal antibodies to DPRP proteins are felt to be useful to diagnose and treat diseases in which they are involved, including cancer.

The expression of DPRP-1 in specialized epithelial cells of a number of tissues suggests that DPRP-1 and other DPRP proteins may be involved in growth and differentiation thereof. Testing using inhibitors described in Example 6 in *in vitro* models of prostate and testis cancer (Example 7) showed that DPRP-1/DPRP-2 inhibitors caused a 50-60% increase in proliferation of PC3 cells at nM concentrations as shown in FIGS. 4A-4C.

Although the invention has been described in accordance with its preferred embodiments, which constitute the best mode presently known to the inventors, it should be understood that changes and modifications as would be obvious to those skilled in this art may be made without departing from its scope which is set forth in the claims appended hereto. For example, although the disclosure focuses on DPRP-1 and DPRP-2 in certain instances, DPRP-3 and its fragments are considered to be similarly useful, as are nucleic acids encoding same. The disclosures of all patents hereinbefore set forth are expressly incorporated herein by reference. Particular features of the invention are emphasized in the claims that follow.

Sequence Listing Summary

SEQ ID.

1. DPRP1 a.a sequence
2. DPRP1 DNA sequence
3. DPRP2 a.a. sequence
4. DPRP2 DNA sequence
5. DPRP-3 a.a. sequence
6. DPRP-3 DNA sequence
7. DPRP-1 transcript 0 a.a.. sequence
8. DPRP-1 transcript 0 DNA sequence
9. DPRP-1 transcript 1 a.a. sequence
10. DPRP-1 transcript 1 DNA sequence
11. DPRP-1 transcript 2 a.a. sequence
12. DPRP-1 transcript 2 DNA sequence
13. DPRP-1 transcript 3 a.a. sequence
14. DPRP-1 transcript 3 DNA sequence
15. DPRP-1 transcript 4 a.a. sequence
16. DPRP-1 transcript 4 DNA sequence
17. DPRP-1 transcript 5 a.a. sequence
18. DPRP-1 transcript 5 DNA sequence
19. DPRP-1 transcript 6 a.a. sequence
20. DPRP-1 transcript 6 DNA sequence
21. DPRP-1 transcript 7 a.a. sequence
22. DPRP-1 transcript 7 DNA sequence
23. DPRP-2 transcript 0 a.a. sequence
24. DPRP-2 transcript 0 DNA sequence
25. DPRP-2 transcript 1 a.a. sequence
26. DPRP-2 transcript 1 DNA sequence
27. DPRP-2 transcript 2 a.a. sequence
28. DPRP-2 transcript 2 DNA sequence
29. DPRP-2 transcript 3 a.a. sequence
30. DPRP-2 transcript 3 DNA sequence
31. DPRP-2 transcript 4 a.a. sequence
32. DPRP-2 transcript 4 DNA sequence

33. DPRP-2 transcript 5 a.a. sequence
34. DPRP-2 transcript 5 DNA sequence
35. DPRP-2 transcript 6 a.a. sequence
36. DPRP-2 transcript 6 DNA sequence
37. DPRP-2 transcript 7 a.a. sequence
38. DPRP-2 transcript 7 DNA sequence
39. DPRP-2 transcript 8 a.a. sequence
40. DPRP-2 transcript 8 DNA sequence
41. DPRP-3 transcript 0 a.a. sequence
42. DPRP-3 transcript 0 DNA. Sequence
43. DPRP-3 transcript 1 a.a. sequence
44. DPRP-3 transcript 1 DNA sequence
45. DPRP1 forward primer used for cloning
46. DPRP1 reverse primer used for cloning full length gene
47. DPRP1 reverse primer used for cloning fusion gene
48. DPRP1 forward primer used for expression profiling
49. DPRP1 reverse primer used for expression profiling
50. DPRP2 forward primer used for cloning
51. DPRP2 reverse primer used for cloning full length gene
52. DPRP2 reverse primer used for cloning fusion gene
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54. DPRP2 reverse primer used for expression profiling
55. DPRP3 forward primer used for cloning
56. DPRP3 reverse primer used for cloning full length gene
57. DPRP3 forward primer used for cloning fusion gene
58. DPRP3 reverse primer used for cloning fusion gene
59. DPRP1 peptide antigen sequences
60. DPRP2 peptide antigen sequences
61. DPRP3 peptide antigen sequences

SEQUENCE LISTING

<110> Qi, Steve
Akinsanya, Karen
Riviere, Pierre
Junien, Jean-Louis

<120> NOVEL SERINE PROTEASE GENES RELATED TO DPPIV

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<151> 2000-10-12

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Asp Glu Asn Val His Phe Ala His Thr Ser Ile Leu Leu Ser Phe Leu
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Leu Ile Leu His Gly Phe Leu Asp Glu Asn Val His Phe Phe His Thr
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Asn Phe Leu Val Ser Gln Leu Ile Arg Ala Gly Lys Pro Tyr Gln Leu
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Val Val Ala Pro Ile Thr Asp Leu Lys Leu Tyr Ala Ser Ala Phe Ser
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Glu Arg Tyr Leu Gly Met Pro Ser Lys Glu Glu Ser Thr Tyr Gln Ala
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Ala Ser Val Leu His Asn Val His Gly Leu Lys Glu Glu Asn Ile Leu
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Ile Ile His Gly Thr Ala Asp Thr Lys Val His Phe Gln His Ser Ala
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Glu Leu Ile Lys His Leu Ile Lys Ala Gly Val Asn Tyr Thr Met Gln
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Val Tyr Pro Asp Glu Gly His Asn Val Ser Glu Lys Ser Lys Tyr His
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Glu Pro Phe Tyr Val Glu Arg Tyr Ser Trp Ser Gln Leu Lys Lys Leu
        35                  40                  45
Leu Ala Asp Thr Arg Lys Tyr His Gly Tyr Met Met Ala Lys Ala Pro
    50                  55                  60
His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
65                  70                  75                  80
Asp Arg Ile Tyr Tyr Leu Ala Met Ser Gly Glu Asn Arg Glu Asn Thr
                85                  90                  95
Leu Phe Tyr Ser Glu Ile Pro Lys Thr Ile Asn Arg Ala Ala Val Leu
            100                 105                 110
Met Leu Ser Trp Lys Pro Leu Leu Asp Leu Phe Gln Ala Thr Leu Asp
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Tyr Gly Met Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg Lys Arg
    130                 135                 140
Ile Gly Thr Val Gly Ile Ala Ser Tyr Asp Tyr His Gln Gly Ser Gly
145                 150                 155                 160
Thr Phe Leu Phe Gln Ala Gly Ser Gly Ile Tyr His Val Lys Asp Gly
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Gly Pro Gln Gly Phe Thr Gln Gln Pro Leu Arg Pro Asn Leu Val Glu
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Pro Asp Trp Ile Ala Phe Ile His Ser Asn Asp Ile Trp Ile Ser Asn
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Ile Val Thr Arg Glu Glu Arg Arg Leu Thr Tyr Val His Asn Glu Leu
225                 230                 235                 240
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Leu Gln Glu Glu Phe Asp Arg Tyr Ser Gly Tyr Trp Trp Cys Pro Lys
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Asn Pro His Cys Val Ser Leu Tyr Lys Leu Ser Ser Pro Glu Asp Asp
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Leu Ala Asp Thr Arg Lys Tyr His Gly Tyr Met Met Ala Lys Ala Pro
50 55 60
His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
65 70 75 80
Asp Arg Ile Tyr Tyr Leu Ala Met Ser Gly Glu Asn Arg Glu Asn Thr
85 90 95
Leu Phe Tyr Ser Glu Ile Pro Lys Thr Ile Asn Arg Ala Ala Val Leu
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Met Leu Ser Trp Lys Pro Leu Leu Asp Leu Phe Gln Ala Thr Leu Asp
115 120 125
Tyr Gly Met Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg Lys Arg
130 135 140
Ile Gly Thr Val Gly Ile Ala Ser Tyr Asp Tyr His Gln Gly Ser Gly
145 150 155 160
Thr Phe Leu Phe Gln Ala Gly Ser Gly Ile Tyr His Val Lys Asp Gly
165 170 175
Gly Pro Gln Gly Phe Thr Gln Gln Pro Leu Arg Pro Asn Leu Val Glu
180 185 190
Thr Ser Cys Pro Asn Ile Arg Met Asp Pro Lys Leu Cys Pro Ala Asp
195 200 205
Pro Asp Trp Ile Ala Phe Ile His Ser Asn Asp Ile Trp Ile Ser Asn
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<210> 10
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Glu Pro Phe Tyr Val Glu Arg Tyr Ser Trp Ser Gln Leu Lys Lys Leu
        35                  40                  45
Leu Ala Asp Thr Arg Lys Tyr His Gly Tyr Met Met Ala Lys Ala Pro
    50                  55                  60
His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
65                  70                  75                  80
Asp Arg Ile Tyr Tyr Leu Ala Met Ser Gly Glu Asn Arg Glu Asn Thr
                85                  90                  95
Leu Phe Tyr Ser Glu Ile Pro Lys Thr Ile Asn Arg Ala Ala Val Leu
            100                 105                 110
Met Leu Ser Trp Lys Pro Leu Leu Asp Leu Phe Gln Ala Thr Leu Asp
        115                 120                 125
Tyr Gly Met Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg Lys Arg
    130                 135                 140
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Thr Phe Leu Phe Gln Ala Gly Ser Gly Ile Tyr His Val Lys Asp Gly
                165                 170                 175
Gly Pro Gln Gly Phe Thr Gln Gln Pro Leu Arg Pro Asn Leu Val Glu
            180                 185                 190
Thr Ser Cys Pro Asn Ile Arg Met Asp Pro Lys Leu Cys Pro Ala Asp
        195                 200                 205
Pro Asp Trp Ile Ala Phe Ile His Ser Asn Asp Ile Trp Ile Ser Asn
    210                 215                 220
Ile Val Thr Arg Glu Glu Arg Arg Leu Thr Tyr Val His Asn Glu Leu
225                 230                 235                 240
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Ile Gln Val Asp Glu Val Arg Arg Leu Val Tyr Phe Glu Gly Thr Lys
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Asp Ser Pro Leu Glu His His Leu Tyr Val Val Ser Tyr Val Asn Pro
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Gly Glu Val Thr Arg Leu Thr Asp Arg Gly Tyr Ser His Ser Cys Cys
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Ile Ser Gln His Cys Asp Phe Phe Ile Ser Lys Tyr Ser Asn Gln Lys
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Asn Pro His Cys Val Ser Leu Tyr Lys Leu Ser Ser Pro Glu Asp Asp
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Pro Thr Cys Lys Thr Lys Glu Phe Trp Ala Thr Ile Leu Asp Ser Ala
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Leu Ala Asp Thr Arg Lys Tyr His Gly Tyr Met Met Ala Lys Ala Pro
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His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
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Leu Phe Tyr Ser Glu Ile Pro Lys Thr Ile Asn Arg Ala Ala Val Leu
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Pro Asp Trp Ile Ala Phe Ile His Ser Asn Asp Ile Trp Ile Ser Asn
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Ile Val Thr Arg Glu Glu Arg Arg Leu Thr Tyr Val His Asn Glu Leu
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Leu Gln Glu Glu Phe Asp Arg Tyr Ser Gly Tyr Trp Trp Cys Pro Lys
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Ala Glu Thr Thr Pro Ser Gly Gly Lys Ile Leu Arg Ile Leu Tyr Glu
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Glu Asn Asp Glu Ser Glu Val Glu Ile Ile His Val Thr Ser Pro Met
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Leu Glu Thr Arg Arg Ala Asp Ser Phe Arg Tyr Pro Lys Thr Gly Thr
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<213> Homo sapiens
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20 25 30
Glu Pro Phe Tyr Val Glu Arg Tyr Ser Trp Ser Gln Leu Lys Lys Leu
35 40 45
Leu Ala Asp Thr Arg Lys Tyr His Gly Tyr Met Met Ala Lys Ala Pro
50 55 60
His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
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<212> DNA
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20 25 30
Glu Pro Phe Tyr Val Glu Arg Tyr Ser Trp Ser Gln Leu Lys Lys Leu
35 40 45
Leu Ala Asp Thr Arg Lys Tyr His Gly Tyr Met Met Ala Lys Ala Pro
50 55 60
His Asp Phe Met Phe Val Lys Arg Asn Asp Pro Asp Gly Pro His Ser
65 70 75 80
Asp Arg Ile Tyr Tyr Leu Ala Met Ser Gly Glu Asn Arg Glu Asn Thr
85 90 95
Leu Phe Tyr Ser Glu Ile Pro Lys Thr Ile Asn Arg Ala Ala Val Leu
100 105 110

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Tyr Gly Met Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg Lys Arg
    130                 135                 140
Ile Gly Thr Val Gly Ile Ala Ser Tyr Asp Tyr His Gln Gly Ser Gly
145                 150                 155                 160
Thr Phe Leu Phe Gln Ala Gly Ser Gly Ile Tyr His Val Lys Asp Gly
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            180                 185                 190
Cys Ala
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<212> DNA
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<210> 19
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<212> PRT
<213> Homo sapiens
<400> 19

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Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
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Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
165 170 175
Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
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Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
195 200 205

Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
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Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp Leu Trp Val
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Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln
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Pro Asp Asp Asp Pro Leu His Lys Gln Pro Arg Phe Trp Ala Ser Met
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Met Glu Ala Ala Ser Cys Pro Pro Asp Tyr Val Pro Pro Glu Ile Phe
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His Phe His Thr Arg Ser Asp Val Arg Leu Tyr Gly Met Ile Tyr Lys
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Pro His Ala Leu Gln Pro Gly Lys Lys His Pro Thr Val Leu Phe Val
660 665 670

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Tyr Gly Gly Pro Gln Val Gln Leu Val Asn Asn Ser Phe Lys Gly Ile
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Lys Tyr Leu Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr Ala Val Val
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Val Ile Asp Gly Arg Gly Ser Cys Gln Arg Gly Leu Arg Phe Glu Gly
705                 710                 715                 720
Ala Leu Lys Asn Gln Met Gly Gln Val Glu Ile Glu Asp Gln Val Glu
                725                 730                 735
Gly Leu Gln Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp Leu Ser Arg
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Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser Leu Met Gly
        755                 760                 765
Leu Ile His Lys Pro Gln Val Phe Lys Val Ala Ile Ala Gly Ala Pro
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Val Thr Val Trp Met Ala Tyr Asp Thr Gly Tyr Thr Glu Arg Tyr Met
785                 790                 795                 800
Asp Val Pro Glu Asn Asn Gln His Gly Tyr Glu Ala Gly Ser Val Ala
                805                 810                 815
Leu His Val Glu Lys Leu Pro Asn Glu Pro Asn Arg Leu Leu Ile Leu
            820                 825                 830
His Gly Phe Leu Asp Glu Asn Val His Phe Phe His Thr Asn Phe Leu
        835                 840                 845
Val Ser Gln Leu Ile Arg Ala Gly Lys Pro Tyr Gln Leu Gln Ile Tyr
    850                 855                 860
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<210> 24
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<210> 25
<211> 518
<212> PRT
<213> Homo sapiens
<400> 25

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Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
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His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu
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Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
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Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
    130                 135                 140
Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
145                 150                 155                 160
Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
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Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
            180                 185                 190
Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
        195                 200                 205
Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
    210                 215                 220
Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp Leu Trp Val
225                 230                 235                 240
Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln
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Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly Val Ala Thr
            260                 265                 270
Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr Trp Trp Cys
        275                 280                 285
Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr Leu Arg Ile
    290                 295                 300
Leu Tyr Glu Glu Val Asp Glu Ser Glu Val Glu Val Ile His Val Pro
305                 310                 315                 320
Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg Tyr Pro Arg
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Thr Gly Ser Lys Asn Pro Lys Ile Ala Leu Lys Leu Ala Glu Phe Gln
            340                 345                 350
Thr Asp Ser Gln Gly Lys Ile Val Ser Thr Gln Glu Lys Glu Leu Val
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Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile Ala Arg Ala
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Gly Trp Thr Arg Asp Gly Lys Tyr Ala Trp Ala Met Phe Leu Asp Arg
385                 390                 395                 400
Pro Gln Gln Trp Leu Gln Leu Val Leu Leu Pro Pro Ala Leu Phe Ile
                405                 410                 415
Pro Ser Thr Glu Asn Glu Glu Gln Arg Leu Ala Ser Ala Arg Ala Val
            420                 425                 430
Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val Thr Asn Val
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Trp Ile Asn Val His Asp Ile Phe Tyr Pro Phe Pro Gln Ser Glu Gly
    450                 455                 460
Glu Asp Glu Leu Cys Phe Leu Arg Ala Asn Glu Cys Lys Thr Gly Phe
465                 470                 475                 480
Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
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Ala Val Asp Ser Ser Arg
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<210> 26
<211> 2411
<212> DNA
<213> Homo sapiens
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<210> 27
<211> 892
<212> PRT
<213> Homo sapiens
<400> 27

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Thr Gly Thr Pro Thr Ala Asp Arg Gly Asp Ala Ala Ala Thr Asp Asp
        35                  40                  45
Pro Ala Ala Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg
    50                  55                  60
Ser Ile Ile His Gly Ser Arg Lys Tyr Ser Gly Leu Ile Val Asn Lys
65                  70                  75                  80
Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
                85                  90                  95
His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu
            100                 105                 110
Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
        115                 120                 125
Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
    130                 135                 140
Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
145                 150                 155                 160
Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
                165                 170                 175
Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
            180                 185                 190
Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
        195                 200                 205
Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
    210                 215                 220
Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp Leu Trp Val
225                 230                 235                 240
Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln
                245                 250                 255
Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly Val Ala Thr
            260                 265                 270
Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr Trp Trp Cys
        275                 280                 285
Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr Leu Arg Ile
    290                 295                 300
Leu Tyr Glu Glu Val Asp Glu Ser Glu Val Glu Val Ile His Val Pro
305                 310                 315                 320
Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg Tyr Pro Arg
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Thr Gly Ser Lys Asn Pro Lys Ile Ala Leu Lys Leu Ala Glu Phe Gln
            340                 345                 350
Thr Asp Ser Gln Gly Lys Ile Val Ser Thr Gln Glu Lys Glu Leu Val
        355                 360                 365
Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile Ala Arg Ala
    370                 375                 380
Gly Trp Thr Arg Asp Gly Lys Tyr Ala Trp Ala Met Phe Leu Asp Arg
385                 390                 395                 400
Pro Gln Gln Trp Leu Gln Leu Val Leu Leu Pro Pro Ala Leu Phe Ile
                405                 410                 415
Pro Ser Thr Glu Asn Glu Glu Gln Arg Leu Ala Ser Ala Arg Ala Val
            420                 425                 430
Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val Thr Asn Val
        435                 440                 445
Trp Ile Asn Val His Asp Ile Phe Tyr Pro Phe Pro Gln Ser Glu Gly
    450                 455                 460
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Glu Asp Glu Leu Cys Phe Leu Arg Ala Asn Glu Cys Lys Thr Gly Phe
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Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
485 490 495
Trp Ser Glu Pro Phe Ser Pro Gly Glu Asp Glu Phe Lys Cys Pro Ile
500 505 510
Lys Glu Glu Ile Ala Leu Thr Ser Gly Glu Trp Glu Val Leu Ala Arg
515 520 525
His Gly Ser Lys Ile Trp Val Asn Glu Glu Thr Lys Leu Val Tyr Phe
530 535 540
Gln Gly Thr Lys Asp Thr Pro Leu Glu His His Leu Tyr Val Val Ser
545 550 555 560
Tyr Glu Ala Ala Gly Glu Ile Val Arg Leu Thr Thr Pro Gly Phe Ser
565 570 575
His Ser Cys Ser Met Ser Gln Asn Phe Asp Met Phe Val Ser His Tyr
580 585 590
Ser Ser Val Ser Thr Pro Pro Cys Val His Val Tyr Lys Leu Ser Gly
595 600 605
Pro Asp Asp Asp Pro Leu His Lys Gln Pro Arg Phe Trp Ala Ser Met
610 615 620
Met Glu Ala Ala Ser Cys Pro Pro Asp Tyr Val Pro Pro Glu Ile Phe
625 630 635 640
His Phe His Thr Arg Ser Asp Val Arg Leu Tyr Gly Met Ile Tyr Lys
645 650 655
Pro His Ala Leu Gln Pro Gly Lys Lys His Pro Thr Val Leu Phe Val
660 665 670
Tyr Gly Gly Pro Gln Val Gln Leu Val Asn Asn Ser Phe Lys Gly Ile
675 680 685
Lys Tyr Leu Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr Ala Val Val
690 695 700
Val Ile Asp Gly Arg Gly Ser Cys Gln Arg Gly Leu Arg Phe Glu Gly
705 710 715 720
Ala Leu Lys Asn Gln Met Gly Gln Val Glu Ile Glu Asp Gln Val Glu
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Gly Leu Gln Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp Leu Ser Arg
740 745 750
Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser Leu Met Gly
755 760 765
Leu Ile His Lys Pro Gln Val Phe Lys Val Ala Ile Ala Gly Ala Pro
770 775 780
Val Thr Val Trp Met Ala Tyr Asp Thr Gly Tyr Thr Glu Arg Tyr Met
785 790 795 800
Asp Val Pro Glu Asn Asn Gln His Gly Tyr Glu Ala Gly Ser Val Ala
805 810 815
Leu His Val Glu Lys Leu Pro Asn Glu Pro Asn Arg Leu Leu Ile Leu
820 825 830
His Gly Phe Leu Asp Glu Asn Val His Phe Phe His Thr Asn Phe Leu
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Val Ser Gln Leu Ile Arg Ala Gly Lys Pro Tyr Gln Leu Gln Ile Tyr
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Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
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His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu
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Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
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Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
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Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
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Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
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Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
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Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
        195                 200                 205
Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
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Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp Leu Trp Val
225                 230                 235                 240
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Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly Val Ala Thr
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Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile Ala Arg Ala
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Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
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Pro His Ala Leu Gln Pro Gly Lys Lys His Pro Thr Val Leu Phe Val
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Lys Tyr Leu Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr Ala Val Val
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Val Ile Asp Gly Arg Gly Ser Cys Gln Arg Gly Leu Arg Phe Glu Gly
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Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser Leu Met Gly
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Leu Ile His Lys Pro Gln Val Phe Lys Ala Gln Pro Leu Ala Tyr Pro
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Pro Arg Leu Pro Gly Arg Lys Arg Ala Leu Phe Pro His Lys Leu Pro
785                 790                 795                 800
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Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
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245 250 255
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Tyr Glu Ala Ala Gly Glu Ile Val Arg Leu Thr Thr Pro Gly Phe Ser
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Pro Asp Asp Asp Pro Leu His Lys Gln Pro Arg Phe Trp Ala Ser Met
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Lys Tyr Leu Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr Ala Val Val
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Ala Leu Lys Asn Gln Met Gly Gln Val Glu Ile Glu Asp Gln Val Glu
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Gly Leu Gln Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp Leu Ser Arg
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Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser Leu Met Gly
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Leu Ile His Lys Pro Gln Val Phe Lys Ala Gln Pro Leu Ala Tyr Pro
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Pro Arg Leu Pro Gly Arg Lys Arg Ala Leu Phe Pro His Lys Leu Pro
785                 790                 795                 800
Arg Leu Pro Thr Asp Pro Ser Arg Glu Thr Leu Pro Ala Pro Asp Leu
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<210> 32
<211> 4076
<212> DNA
<213> Homo sapiens
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<210> 33
<211> 879
<212> PRT
<213> Homo sapiens
<400> 33

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35 40 45
Pro Ala Ala Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg
50 55 60
Ser Ile Ile His Gly Ser Arg Lys Tyr Ser Gly Leu Ile Val Asn Lys
65 70 75 80
Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
85 90 95

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His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu
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Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
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Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
    130                 135                 140
Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
145                 150                 155                 160
Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
                165                 170                 175
Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
            180                 185                 190
Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
        195                 200                 205
Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
    210                 215                 220
Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp Leu Trp Val
225                 230                 235                 240
Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln
                245                 250                 255
Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly Val Ala Thr
            260                 265                 270
Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr Trp Trp Cys
        275                 280                 285
Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr Leu Arg Ile
    290                 295                 300
Leu Tyr Glu Glu Val Asp Glu Ser Glu Val Glu Val Ile His Val Pro
305                 310                 315                 320
Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg Tyr Pro Arg
                325                 330                 335
Thr Gly Ser Lys Asn Pro Lys Ile Ala Leu Lys Leu Ala Glu Phe Gln
            340                 345                 350
Thr Asp Ser Gln Gly Lys Ile Val Ser Thr Gln Glu Lys Glu Leu Val
        355                 360                 365
Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile Ala Arg Ala
    370                 375                 380
Gly Trp Thr Arg Asp Gly Lys Tyr Ala Trp Ala Met Phe Leu Asp Arg
385                 390                 395                 400
Pro Gln Gln Trp Leu Gln Leu Val Leu Leu Pro Pro Ala Leu Phe Ile
                405                 410                 415
Pro Ser Thr Glu Asn Glu Glu Gln Arg Leu Ala Ser Ala Arg Ala Val
            420                 425                 430
Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val Thr Asn Val
        435                 440                 445
Trp Ile Asn Val His Asp Ile Phe Tyr Pro Phe Pro Gln Ser Glu Gly
    450                 455                 460
Glu Asp Glu Leu Cys Phe Leu Arg Ala Asn Glu Cys Lys Thr Gly Phe
465                 470                 475                 480
Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
                485                 490                 495
Trp Ser Glu Pro Phe Ser Pro Gly Glu Asp Glu Phe Lys Cys Pro Ile
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Lys Glu Glu Ile Ala Leu Thr Ser Gly Glu Trp Glu Val Leu Ala Arg
        515                 520                 525
His Gly Ser Lys Gly Thr Lys Asp Thr Pro Leu Glu His His Leu Tyr
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Val Val Ser Tyr Glu Ala Ala Gly Glu Ile Val Arg Leu Thr Thr Pro
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Gly Phe Ser His Ser Cys Ser Met Ser Gln Asn Phe Asp Met Phe Val
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Leu Ser Gly Pro Asp Asp Asp Pro Leu His Lys Gln Pro Arg Phe Trp
        595                 600                 605
Ala Ser Met Met Glu Ala Ala Ser Cys Pro Pro Asp Tyr Val Pro Pro
    610                 615                 620
Glu Ile Phe His Phe His Thr Arg Ser Asp Val Arg Leu Tyr Gly Met
625                 630                 635                 640
Ile Tyr Lys Pro His Ala Leu Gln Pro Gly Lys Lys His Pro Thr Val
                645                 650                 655
Leu Phe Val Tyr Gly Gly Pro Gln Val Gln Leu Val Asn Asn Ser Phe
            660                 665                 670
Lys Gly Ile Lys Tyr Leu Arg Leu Asn Thr Leu Ala Ser Leu Gly Tyr
        675                 680                 685
Ala Val Val Val Ile Asp Gly Arg Gly Ser Cys Gln Arg Gly Leu Arg
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Phe Glu Gly Ala Leu Lys Asn Gln Met Gly Gln Val Glu Ile Glu Asp
705                 710                 715                 720
Gln Val Glu Gly Leu Gln Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp
                725                 730                 735
Leu Ser Arg Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser
            740                 745                 750
Leu Met Gly Leu Ile His Lys Pro Gln Val Phe Lys Val Ala Ile Ala
        755                 760                 765
Gly Ala Pro Val Thr Val Trp Met Ala Tyr Asp Thr Gly Tyr Thr Glu
    770                 775                 780
Arg Tyr Met Asp Val Pro Glu Asn Asn Gln His Gly Tyr Glu Ala Gly
785                 790                 795                 800
Ser Val Ala Leu His Val Glu Lys Leu Pro Asn Glu Pro Asn Arg Leu
                805                 810                 815
Leu Ile Leu His Gly Phe Leu Asp Glu Asn Val His Phe Phe His Thr
            820                 825                 830
Asn Phe Leu Val Ser Gln Leu Ile Arg Ala Gly Lys Pro Tyr Gln Leu
        835                 840                 845
Gln Ile Tyr Pro Asn Glu Arg His Ser Ile Arg Cys Pro Glu Ser Gly
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Glu His Tyr Glu Val Thr Leu Leu His Phe Leu Gln Glu Tyr Leu
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<210> 34
<211> 4263
<212> DNA
<213> Homo sapiens
<400> 34

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<210> 35
<211> 879
<212> PRT
<213> Homo sapiens
<400> 35

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Thr Gly Thr Pro Thr Ala Asp Arg Gly Asp Ala Ala Ala Thr Asp Asp
        35                  40                  45
Pro Ala Ala Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg
    50                  55                  60
Ser Ile Ile His Gly Ser Arg Lys Tyr Ser Gly Leu Ile Val Asn Lys
65                  70                  75                  80
Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
                85                  90                  95
His Ser His Arg Leu Tyr Tyr Leu Gly Met Pro Tyr Gly Ser Arg Glu
            100                 105                 110
Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
        115                 120                 125
Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
    130                 135                 140
Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
145                 150                 155                 160
Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
                165                 170                 175
Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
            180                 185                 190
Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
        195                 200                 205
Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
    210                 215                 220
Ala Asp Pro Ala Phe Phe Ser Phe Ile Asn Asn Ser Asp Leu Trp Val
225                 230                 235                 240
Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln
                245                 250                 255
Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly Val Ala Thr
            260                 265                 270
Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr Trp Trp Cys
        275                 280                 285
Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr Leu Arg Ile
    290                 295                 300
Leu Tyr Glu Glu Val Asp Glu Ser Glu Val Glu Val Ile His Val Pro
305                 310                 315                 320
Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg Tyr Pro Arg
                325                 330                 335
Thr Gly Ser Lys Asn Pro Lys Ile Ala Leu Lys Leu Ala Glu Phe Gln
            340                 345                 350
Thr Asp Ser Gln Gly Lys Ile Val Ser Thr Gln Glu Lys Glu Leu Val
        355                 360                 365
Gln Pro Phe Ser Ser Leu Phe Pro Lys Val Glu Tyr Ile Ala Arg Ala
    370                 375                 380
Gly Trp Thr Arg Asp Gly Lys Tyr Ala Trp Ala Met Phe Leu Asp Arg
385                 390                 395                 400
Pro Gln Gln Trp Leu Gln Leu Val Leu Leu Pro Pro Ala Leu Phe Ile
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Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val Thr Asn Val
        435                 440                 445
Trp Ile Asn Val His Asp Ile Phe Tyr Pro Phe Pro Gln Ser Glu Gly
    450                 455                 460
Glu Asp Glu Leu Cys Phe Leu Arg Ala Asn Glu Cys Lys Thr Gly Phe
465                 470                 475                 480
Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
                485                 490                 495
Trp Ser Glu Pro Phe Ser Pro Gly Glu Asp Glu Phe Lys Cys Pro Ile
            500                 505                 510
Lys Glu Glu Ile Ala Leu Thr Ser Gly Glu Trp Glu Val Leu Ala Arg
        515                 520                 525
His Gly Ser Lys Gly Thr Lys Asp Thr Pro Leu Glu His His Leu Tyr
    530                 535                 540
Val Val Ser Tyr Glu Ala Ala Gly Glu Ile Val Arg Leu Thr Thr Pro
545                 550                 555                 560
Gly Phe Ser His Ser Cys Ser Met Ser Gln Asn Phe Asp Met Phe Val
                565                 570                 575
Ser His Tyr Ser Ser Val Ser Thr Pro Pro Cys Val His Val Tyr Lys
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Pro Ala Ala Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg
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Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
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Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
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Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
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Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
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Asp Gly Gly Lys Asn Gly Phe Met Val Ser Pro Met Lys Pro Leu Glu
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Ile Lys Thr Gln Cys Ser Gly Pro Arg Met Asp Pro Lys Ile Cys Pro
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Leu Ser Arg Val Ala Ile His Gly Trp Ser Tyr Gly Gly Phe Leu Ser
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Ala Tyr Pro Pro Arg Leu Pro Gly Arg Lys Arg Ala Leu Phe Pro His
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Pro Ala Ala Arg Phe Gln Val Gln Lys His Ser Trp Asp Gly Leu Arg
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Ser Ile Ile His Gly Ser Arg Lys Tyr Ser Gly Leu Ile Val Asn Lys
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Ala Pro His Asp Phe Gln Phe Val Gln Lys Thr Asp Glu Ser Gly Pro
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Asn Ser Leu Leu Tyr Ser Glu Ile Pro Lys Lys Val Arg Lys Glu Ala
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Leu Leu Leu Leu Ser Trp Lys Gln Met Leu Asp His Phe Gln Ala Thr
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Pro His His Gly Val Tyr Ser Arg Glu Glu Glu Leu Leu Arg Glu Arg
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Lys Arg Leu Gly Val Phe Gly Ile Thr Ser Tyr Asp Phe His Ser Glu
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Ser Gly Leu Phe Leu Phe Gln Ala Ser Asn Ser Leu Phe His Cys Arg
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Ala Asn Ile Glu Thr Gly Glu Glu Arg Arg Leu Thr Phe Cys His Gln
245 250 255
Gly Leu Ser Asn Val Leu Asp Asp Pro Lys Ser Ala Gly Val Ala Thr
260 265 270
Phe Val Ile Gln Glu Glu Phe Asp Arg Phe Thr Gly Tyr Trp Trp Cys
275 280 285
Pro Thr Ala Ser Trp Glu Gly Ser Glu Gly Leu Lys Thr Leu Arg Ile
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Leu Tyr Glu Glu Val Asp Glu Ser Glu Val Glu Val Ile His Val Pro
305 310 315 320
Ser Pro Ala Leu Glu Glu Arg Lys Thr Asp Ser Tyr Arg Tyr Pro Arg
325 330 335
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Pro Arg Asn Val Gln Pro Tyr Val Val Tyr Glu Glu Val Thr Asn Val
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Glu Asp Glu Leu Cys Phe Leu Arg Ala Asn Glu Cys Lys Thr Gly Phe
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Cys His Leu Tyr Lys Val Thr Ala Val Leu Lys Ser Gln Gly Tyr Asp
485 490 495
Trp Ser Glu Pro Phe Ser Pro Gly Glu Asp Glu Phe Lys Cys Pro Ile
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Lys Glu Glu Ile Ala Leu Thr Ser Gly Glu Trp Glu Val Leu Ala Arg
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His Gly Ser Lys Gly Thr Lys Asp Thr Pro Leu Glu His His Leu Tyr
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Val Val Ser Tyr Glu Ala Ala Gly Glu Ile Val Arg Leu Thr Thr Pro
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Gly Phe Ser His Ser Cys Ser Met Ser Gln Asn Phe Asp Met Phe Val
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Ser His Tyr Ser Ser Val Ser Thr Pro Pro Cys Val His Val Tyr Lys
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Ile Tyr Lys Pro His Ala Leu Gln Pro Gly Lys Lys His Pro Thr Val
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Phe Glu Gly Ala Leu Lys Asn Gln Met Gly Gln Val Glu Ile Glu Asp
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Gln Val Glu Gly Leu Gln Phe Val Ala Glu Lys Tyr Gly Phe Ile Asp
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<212> PRT
<213> Homo sapiens
<400> 41

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Val Leu Leu Ala Tyr Asp Val Lys Gln Ile Phe His Tyr Ser Tyr Thr
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Ala Ser Tyr Val Ile Tyr Asn Ile His Thr Arg Glu Val Trp Glu Leu
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Asn Pro Pro Glu Val Glu Asp Ser Val Leu Gln Tyr Ala Ala Trp Gly
85 90 95
Val Gln Gly Gln Gln Leu Ile Tyr Ile Phe Glu Asn Asn Ile Tyr Tyr
100 105 110

Gln Pro Asp Ile Lys Ser Ser Ser Leu Arg Leu Thr Ser Ser Gly Lys
115 120 125
Glu Glu Ile Ile Phe Asn Gly Ile Ala Asp Trp Leu Tyr Glu Glu Glu
130 135 140
Leu Leu His Ser His Ile Ala His Trp Trp Ser Pro Asp Gly Glu Arg
145 150 155 160
Leu Ala Phe Leu Met Ile Asn Asp Ser Leu Val Pro Thr Met Val Ile
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Pro Arg Phe Thr Gly Ala Leu Tyr Pro Lys Gly Lys Gln Tyr Pro Tyr
180 185 190
Pro Lys Ala Gly Gln Val Asn Pro Thr Ile Lys Leu Tyr Val Val Asn
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Leu Tyr Gly Pro Thr His Thr Leu Glu Leu Met Pro Pro Asp Ser Phe
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Lys Ser Arg Glu Tyr Tyr Ile Thr Met Val Lys Trp Val Ser Asn Thr
225 230 235 240
Lys Thr Val Val Arg Trp Leu Asn Arg Pro Gln Asn Ile Ser Ile Leu
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275 280 285
Arg Asp Gly Ser Lys Phe Phe Met Thr Val Pro Val Lys Gln Gly Gly
290 295 300
Arg Gly Glu Phe His His Ile Ala Met Phe Leu Ile Gln Ser Lys Ser
305 310 315 320
Glu Gln Ile Thr Val Arg His Leu Thr Ser Gly Asn Trp Glu Val Ile
325 330 335
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Gly Leu Leu Asn Arg Gln Cys Ile Ser Cys Asn Phe Met Lys Glu Gln
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Phe Met Asp Arg Asn Gln Tyr Ala Leu Leu Leu Ile Met Asp Glu Glu
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Pro Gly Gly Gln Leu Val Thr Asp Lys Phe His Ile Asp Trp Asp Ser
485 490 495
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Leu Gly Ser Val Glu Val Lys Asp Gln Ile Thr Ala Val Lys Phe Leu
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Leu Lys Leu Pro Tyr Ile Asp Ser Lys Arg Leu Ser Ile Phe Gly Lys
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Gly Tyr Gly Gly Tyr Ile Ala Ser Met Ile Leu Lys Ser Asp Glu Lys
565 570 575

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Lys Glu Glu Asn Ile Leu Ile Ile His Gly Thr Ala Asp Thr Lys Val
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His Phe Gln His Ser Ala Glu Leu Ile Lys His Leu Ile Lys Ala Gly
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Val Asn Tyr Thr Met Gln Val Tyr Pro Asp Glu Gly His Asn Val Ser
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Glu Lys Ser Lys Tyr His Leu Tyr Ser Thr Ile Leu Lys Phe Phe Ser
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<213> Homo sapiens
<400> 43

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35 40 45
Val Leu Leu Ala Tyr Asp Val Lys Gln Ile Phe His Tyr Ser Tyr Thr
50 55 60
Ala Ser Tyr Val Ile Tyr Asn Ile His Thr Arg Glu Val Trp Glu Leu
65 70 75 80

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Val Gln Gly Gln Gln Leu Ile Tyr Ile Phe Glu Asn Asn Ile Tyr Tyr
            100                 105                 110
Gln Pro Asp Ile Lys Ser Ser Ser Leu Arg Leu Thr Ser Ser Gly Lys
        115                 120                 125
Glu Glu Ile Ile Phe Asn Gly Ile Ala Asp Trp Leu Tyr Glu Glu Glu
    130                 135                 140
Leu Leu His Ser His Ile Ala His Trp Trp Ser Pro Asp Gly Glu Arg
145                 150                 155                 160
Leu Ala Phe Leu Met Ile Asn Asp Ser Leu Val Pro Thr Met Val Ile
                165                 170                 175
Pro Arg Phe Thr Gly Ala Leu Tyr Pro Lys Gly Lys Gln Tyr Pro Tyr
            180                 185                 190
Pro Lys Ala Gly Gln Val Asn Pro Thr Ile Lys Leu Tyr Val Val Asn
        195                 200                 205
Leu Tyr Gly Pro Thr His Thr Leu Glu Leu Met Pro Pro Asp Ser Phe
    210                 215                 220
Lys Ser Arg Glu Tyr Tyr Ile Thr Met Val Lys Trp Val Ser Asn Thr
225                 230                 235                 240
Lys Thr Val Val Arg Trp Leu Asn Arg Pro Gln Asn Ile Ser Ile Leu
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Thr Val Cys Glu Thr Thr Thr Gly Ala Cys Ser Lys Lys Tyr Glu Met
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Thr Ser Asp Thr Trp Leu Ser Gln Gln Asn Glu Glu Pro Val Phe Ser
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Arg Asp Gly Ser Lys Phe Phe Met Thr Val Pro Val Lys Gln Gly Gly
    290                 295                 300
Arg Gly Glu Phe His His Ile Ala Met Phe Leu Ile Gln Ser Lys Ser
305                 310                 315                 320
Glu Gln Ile Thr Val Arg His Leu Thr Ser Gly Asn Trp Glu Val Ile
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Lys Ile Leu Ala Tyr Asp Glu Thr Thr Gln Lys Ile Ser Ala Ser Thr
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Glu Gly Leu Leu Asn Arg Gln Cys Ile Ser Cys Asn Phe Met Lys Glu
        355                 360                 365
Gln Cys Thr Tyr Phe Asp Ala Ser Phe Ser Pro Met Asn Gln His Phe
    370                 375                 380
Leu Leu Phe Cys Glu Gly Pro Arg Val Pro Val Val Ser Leu His Ser
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                405                 410                 415
Lys Glu Ala Ile Leu Lys Lys Lys Ile Gly Lys Pro Glu Ile Lys Ile
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Asp Phe Met Asp Arg Asn Gln Tyr Ala Leu Leu Leu Ile Met Asp Glu
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Glu Pro Gly Gly Gln Leu Val Thr Asp Lys Phe His Ile Asp Trp Asp
465                 470                 475                 480
Ser Val Leu Ile Asp Met Asp Asn Val Ile Val Ala Arg Phe Asp Gly
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Arg Gly Ser Gly Phe Gln Gly Leu Lys Ile Leu Gln Glu Ile His Arg
            500                 505                 510
Arg Leu Gly Ser Val Glu Val Lys Asp Gln Ile Thr Ala Val Lys Phe
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Leu Leu Lys Leu Pro Tyr Ile Asp Ser Lys Arg Leu Ser Ile Phe Gly
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Val His Phe Gln His Ser Ala Glu Leu Ile Lys His Leu Ile Lys Ala
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Gly Val Asn Tyr Thr Met Gln Val Tyr Pro Asp Glu Gly His Asn Val
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